PHYSICO-CHEMICAL STUDIES OF AMPHIPHILIC DRUG SYSTEMS

THESIS

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BY

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Dedicated to
my Family

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Certificate

This is to certify that the thesis entitled **"Physico-Chemical Studies of Amphiphilic Drug Systems"** is the original work carried out by **Mr. Gamal Ahmed Abdullah Al-dahbali** under my supervision and is suitable for submission for the award of Ph.D. degree in **Chemistry**.

(Dr. Mohd. Akram)

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List of Publications

(1) **Surface and Solution Properties of Amphiphilic Drug-Nonionic Surfactant Systems**

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(2) **Adsorption and Micellization Behavior of Cationic Surfactants (Gemini and Conventional)–Amphiphilic Drug Systems**

Andleeb Z. Naqvi, **Gamal A. Al-dahbali**, Mohd. Akram and Kabir-ud-Din

J. Solution Chem. (in press).

(3) **Surface and Micellar Properties of Some Amphiphilic Drugs in Different Salt Solutions**

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Colloid J. (in press).

(4) **Physicochemical Studies of Aqueous Amphiphilic Drug + Hydrotrope Solutions**

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Introduction

The word amphiphile was coined by Paul Winsor. It comes from two Greek roots; *amphi* means "double" and *philos* means "affinity". An amphiphilic substance exhibits double affinity, which can be defined from the physico-chemical point of view as a polar-apolar affinity. Amphiphilic compounds bear an ionic (cationic, anionic or zwitterionic) or nonionic polar head group and a nonpolar hydrophobic portion. The polar portion exhibits a strong affinity for polar solvents, particularly water, and it is often called hydrophilic part or hydrophile, while nonpolar is called hydrophobe or liphophile.

The terms amphiphile and surfactant are often used interchangeably. The word surfactant originates from surface-active agent. This points to a key property of surfactants: their tendency to segregate to an air/water interface and consequently to lower the surface tension compared to pure water. The thermodynamic properties of amphiphiles in solution are controlled by the tendency for the hydrophobic region to avoid contact with the water, which has been termed the hydrophobic effect. This leads to the association of molecules into micelles, which are spherical or elongated structures in which the hydrophobic inner core is shielded from water by the surrounding corona formed from the hydrophilic ends of the molecules. The ability of surfactants to self-aggregate depends on its structure, its concentration, the solubilizing media and the method used to preparing the self-assemblies.

Amphiphiles exhibit other properties than tension lowering and this is why they are often labeled according to their main use such as: soap, detergent, wetting

agent, dispersant, emulsifier, foaming agent, bactericide, corrosion inhibitor, antistatic agent, etc., or by the structure they are able to build, i.e., membranes, microemulsions, vesicles, liposomes, etc.

Classification of Surfactants

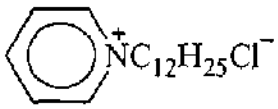
Surfactants are typically classified on the basis of physical properties or functionality and the most important physical property used for classification is ionicity, i.e., surfactant is charged or uncharged. The charged surfactants are further classified on the basis of nature of charge on the head group of hydrophilic moiety.

Cationic surfactants

Cationic surfactants yield a positively charged surfactant ion and a negatively charged counterion upon dissolution in water. Examples include quaternary ammonium salts and amine oxides. Here the surface active head group portion bears a positive charge. The prime use of cationic surfactants is their tendency to adsorb at negatively charged surfaces, e.g., anticorrosive agents for steel, flotation collectors for mineral ores, dispersants for inorganic pigments, antistatic agents and fabric softeners, hair conditioners, anticaking agent for fertilizers and as bactericides.

Examples:

Cetyltrimethylammonium bromide $CH_3(CH_2)_{15}N^+(CH_3)_3Br^-$

Dodecylpyridinium chloride 

Anionic surfactants

These surfactants give rise to a negatively charged surfactant ion and a positively charged counterion (which is, in general, an alkaline metal Na^+, K^+ or quaternary ammonium) upon dissolution in water. They are the most commonly used surfactants in industrial applications [1, 2] due to their relatively low cost of manufacture and they are used in practically every type of detergent. For optimum detergency the hydrophobic chain is a linear alkyl group with a chain length in the region of 12-16 carbon atoms.

Examples:

Sodium dodecyl sulphate $CH_3(CH_2)_{11}OSO_3^- Na^+$

Potassium laurate $CH_3(CH_2)_{10}COO^- K^+$

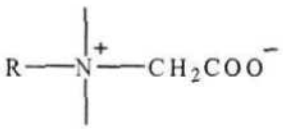
Zwitterionic surfactants

Amphoteric or zwitterionic surfactants can behave as anionic, nonionic, or cationic species, depending on the pH of the solution. In acidic pH solutions, the molecule acquires a positive charge and behaves like a cationic surfactant, where in alkaline pH solutions they become negatively charged and behave like anionic one. Near the so-called isoelectric point, these surfactants display both charges and

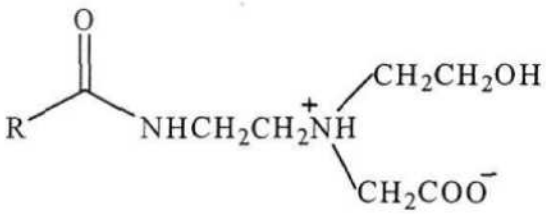
are truly amphoteric, often with a minimum of interfacial activity and concomitant maximum of water solubility. The change in the charge with pH of zwitterionic surfactants affects their properties such as wetting, detergency, foaming, etc. Zwitterionic surfactants, particularly the amino acid ones, are quite biocompatible and are used in pharmaceuticals and cosmetics.

Examples:

Betaines



Imidazolines



Nonionic surfactants

As their name implies, nonionic surfactants contain only electrically neutral head groups. The most common nonionic surfactants are those based on ethylene oxide, which are referred as ethoxylated surfactants [3-5]. These surfactants include several classes such as alcohol ethoxylates, alkyl phenyl ethoxylates, fatty acid ethoxylates, monoalkanol amide ethoxylates, sorbitan ester ethoxylates, etc.

Another important class of nonionics is multi-hydroxy products such as glycolesters/glycerol (and polyglycerol) esters, glucosides (and polyglucosides) and sucrose esters.

Examples:

Alkylphenolethoxylate $CH_3(CH_2)_mC_6H_4\text{-}(CH_2CH_2O)_nOH$

Poly(ethyleneglycol)-*t*-octylphenylether $[t\text{-}C_8H_{17}\text{-}C_6H_4\text{-}(OCH_2CH_2)_nOH]$

Gemini surfactants

Gemini surfactants are surfactants consisting of two hydrophilic and two hydrophobic moieties linked by a spacer at level of or closed to the head [6] (Fig. 1.1). Menger and Littau [6] assigned the name of gemini to bis-surfactants with rigid spacer (i.e., benzene, stilbene). The name was then extended to other bis or double-tailed surfactants, irrespective of the nature of spacers. Geminis were known long before to Bunton et al. [7], who was the first to synthesise gemini surfactants of the bis (quaternary ammonium bromide) type with two C_{16} chains, separated by a spacer having lengths of two, four, or six carbon atoms. Devinsky [8] also synthesized bis (quaternary ammonium) geminis with chain lengths from 6 to 18 carbon atoms and spacer of five carbon atoms long, and reported the micelle formation of these surfactants. The surface properties of geminis were first described by the late Mitsui Okahara of Osaka University and his colleagues [9-13], who synthesized them in their laboratories. A considerable number of investigations have reported on their unusual physicochemical properties,

including their high surface activity [6,13,14], unusual viscosity changes with an increase in surfactant concentration [15], unusual micelle structure [16, 17], aberrant aggregation behavior [18], and stronger interaction with oppositely charged surfactants [19]. The greater efficiency and effectiveness of geminis over comparable conventional surfactants make them cost-effective as well as environmentally desirable. The interest of geminis in academic circles and among scientists at surfactant-producing companies is due to the following reasons:

(i) Their *cmc*, on a weight percent basis, is at least one order of magnitude lower than for the corresponding single tail – single head surfactants.

(ii) They are 10–100 times more efficient at reducing the surface tension of water and the interfacial tension at an oil/water interface than conventional surfactants.

(iii) They appear to have better solubilizing, wetting, foaming, and lime-soap dispersing ability than the conventional surfactants. Some cationic gemini surfactants possess interesting biological properties.

(iv) The aqueous solutions of some gemini surfactants with a short spacer show special rheological properties (viscoelasticity, shear-thickening) at relatively low concentrations.

(v) Gemini surfactants can be synthesized with an enormous variety of structures. In principle, it is possible to connect any two identical or different surfactants among the available ones by a spacer group that can be hydrophilic or hydrophobic, flexible or rigid, heteroatomic, aromatic, etc. Therefore, the

structures and properties of gemini surfactants can be more finely tuned for a given application than for conventional surfactants.

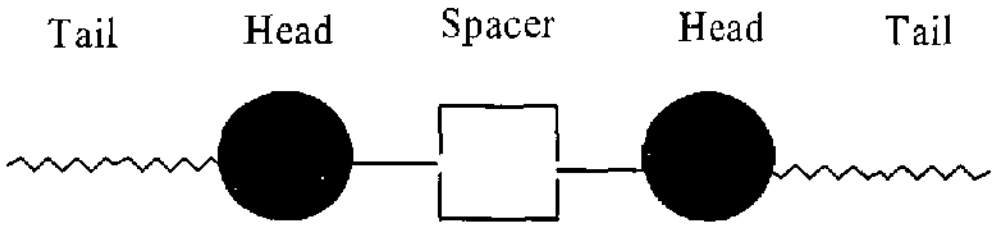


Fig. 1.1: *Structure of gemini surfactant.*

Bolaform surfactants

Bolaform surfactants consist of two hydrophilic head groups, connected by a long hydrocarbon spacer (Fig. 1.2). Their tendency to aggregation is lower, and aggregation numbers are smaller than those of the monomeric surfactants of which they consist.

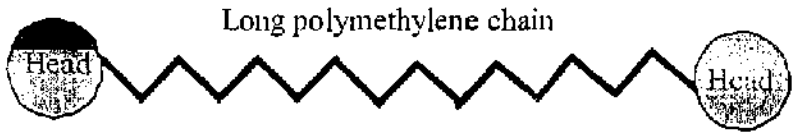


Fig. 1.2: *Schematic representation of a bolaform surfactant.*

Micelle Formation and Critical Micelle Concentration

Since the beginning of the study of surfactant solutions, it was recognized that the physical properties of these solutions, such as surface tension, electrical conductivity and detergency, show an abrupt change in the neighborhood of a

critical concentration: these unusual properties indicated the formation of molecular aggregates. The formation of colloidal sized clusters of individual surfactant molecules in solution is now better known as micellization. The word micelle is a Latin term meaning "small bit" and was coined by J. W. McBain [20] in 1920 to describe colloidal sized particles of detergents and soaps. Micelle formation is primarily controlled by three forces: the hydrophobic repulsion between the hydrocarbon chains and the aqueous solution, the charge repulsion of ionic head groups and the van der Waals attraction between the hydrocarbon tails [21, 22].

The micellization is of primarily an entropy-driven process. When surfactants are dissolved in water, the hydrophobic group disrupts the structure of water and therefore increases the free energy of the system. Surfactant molecules therefore concentrate at interface, so that their hydrophobic groups are directed away from the water and the free energy of the solution is minimized. The distortion of the water structure can also be decreased (and the free energy of the solution reduced) by the aggregation of surface active molecules into micelles with their hydrophobic groups directed towards the interior of micelles and their hydrophilic groups directed towards the water. The micelles first appear in solution at and above the *cmc* [23]. The term *cmc* was established by Davis and Bury [24] in 1930, defining it as the threshold concentration at which micelles first appear in solution. *cmc* is an important property of the surfactants which reflects its micellization ability. The physico-chemical properties of surfactants vary

markedly above and below the *cmc* value [25-28]. Below the *cmc* value, the physico-chemical properties of ionic surfactants (e.g., conductivities, electromotive force) resemble those of strong electrolytes. Above the *cmc* value, these properties change drastically, indicating a highly cooperative association process is taking place. This is illustrated by Preston's [29] classic graph (Fig. 1.3).

Clear breaks of almost every measurable physical property that depends on size and number of particles in solution are shown by all types of surfactants, i.e., nonionic, anionic, cationic and zwitterionic in aqueous media. A wide variety of techniques involving the measurement of physical properties have been used to determine *cmc* value.

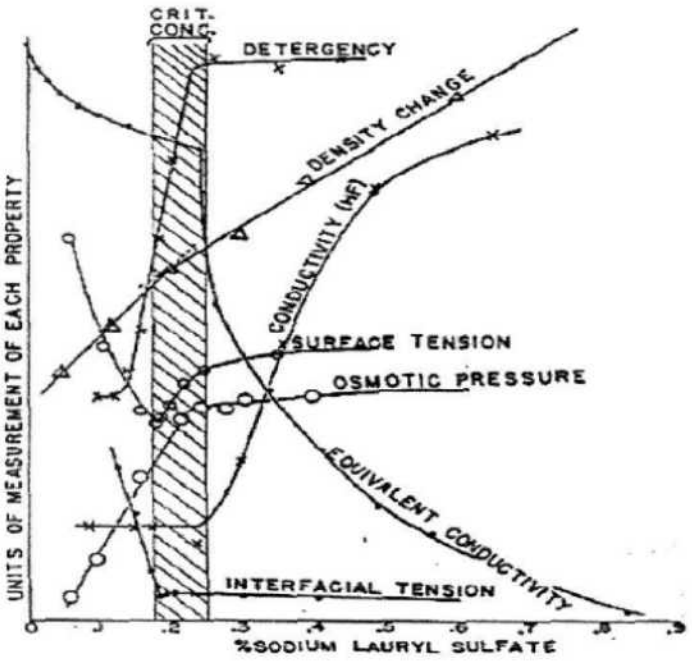


Fig. 1.3: *Preston's classic graph showing variation in physical properties of surfactant solutions below and above the cmc value of sodium dodecyl sulphate.*

Factors Affecting the cmc

Structure of the surfactant

For ionic amphiphiles, increase in the number of carbon atoms in the unbranched hydrocarbon chains leads to a decrease in the *cmc*. As a general rule for ionic surfactants, the *cmc* is halved when the length of the straight hydrocarbon chain is increased by one methylene group, while in case of nonionic surfactants, the addition of one methylene group causes the *cmc* to decrease approximately 1/3 its original value [30]. Muller et al. [31-34] reported that substitution of the CF_3 groups from the terminal CH_3 groups of surfactants hydrocarbon chain roughly doubles the *cmc* and it is also confirmed by Gerry et al. [35] who observed corresponding decrease in aggregation number. A phenyl group that is a part of hydrophobic group with terminal hydrophilic group is equivalent (in its effect on *cmc*) to about three and one-half methylene groups.

In aqueous media, ionic surfactants have a much higher *cmc* than nonionic surfactants with a corresponding hydrocarbon chain, due to the lack of electrical work necessary in forming the micelles.

For usual type of polyoxyethylenated nonionics, the *cmc* decreases with decrease in number of oxyethylene units in the polyoxyethylene chain, since this makes the surfactant more hydrophobic.

Presence of various additives in the solution

(a) Effect of electrolyte

The presence of electrolyte in aqueous solution causes a change in the *cmc*, the effect being more pronounced for anionic and cationic than zwitterionic surfactants and more pronounced for zwitterionics than for nonionics. The effect of concentration of electrolyte on *cmc* of ionic surfactants is given by the following relation [36]

$$\log cmc = - a \log c_i + b \qquad (1.1)$$

where a and b are the constants for a given ionic head at a particular temperature and c_i is the total counterion concentration in equivalents per liter. The depression of the *cmc* in these cases is due mainly to the decrease in the thickness of the ionic atmosphere surrounding the ionic head groups in the presence of the additional electrolyte and the consequent decreased electrical repulsion between them in the micelle. For sodium luarate and sodium naphthenate, the order of decreasing effectiveness of the anion in depressing the *cmc* is $PO_4^{3-} > B_4O_7^{2-} > OH^- > CO_3^{2-} > HCO_3^- > SO_4^{2-} > NO_3^- > Cl^-$ [37].

The change in the *cmc* of nonionics and zwitterionics on the addition of electrolyte has been attributed [38, 39] mainly to the " salting out " or "salting in " of the hydrophobic groups in the aqueous solvent by the electrolyte, rather than to the effect of the latter on the hydrophilic groups of the surfactant. Salting in or

salting out by an ion depends upon whether the ion is a water structure breaker or a water structure maker.

(b) Effect of organic additives

Small amounts of organic materials may produce marked changes in the *cmc* in aqueous media. Knowledge of the effects of these materials, on the *cmc* of surfactants is therefore of great importance both for theoretical and practical purposes. Organic compounds affect the *cmc* either by penetrating into the micellar region, or by modifying solvent-micelle or solvent-monomer interactions. Non-polar compounds, such as hydrocarbons, that are believed to penetrate into the inner portion of the core, decrease the *cmc* only slightly. Addition of longer chain alcohols promotes micelle formation and lowers the *cmc*. The magnitude of *cmc* decrease depends on the alkyl chain length of the organic additive and the hydrophilic group associated with the chain. Urea, formamide, and guanidinium salts are believed to increase the *cmc* of surfactants in aqueous solution because of their disruption of the water structure. These water structure breakers may also increase the *cmc* by increasing the entropy effect accompanying micellization.

Temperature

The influence of temperature on micellization is usually weak, reflecting subtle changes in bonding, heat capacity and volume that accompany the transition. In general, for ionic surfactants, the *cmc* first decreases in the lower

range of temperature; at higher temperature it increases [40]. For nonionic surfactants, the *cmc* decreases with increasing temperature [41]. The decrease in *cmc* of ionic surfactants with temperature increase at lower temperatures is possibly due to dehydration of the monomers, whilst further temperature increase causes disruption of the structured water around the hydrophobic groups which opposes aggregation. Also, thermal agitation of molecules at higher temperatures results in a decreased self-adhesion between molecules.

pH

In amphiphiles containing ionizable group such as $-NH_2$, $-(CH_3)_2 N\rightarrow O$ and – COOH, the degree of dissociation will be dependent on pH [42]. In general, the *cmc* will be high at pH values where the group is charged (low pH for $-NH_2$ and $-(CH_3)_2 N\rightarrow O$ and high pH for –COOH) and low when uncharged. Some zwitterionic surfactants become cationic at low pH, a change that can be accompanied by a rapid rise in the *cmc* [43] or more modest rise [44] depending on structure and hence hydrophilicity of the zwitterionic form.

Pressure

It has been suggested that the amphiphile molecules when present in the micelle are in a more expanded condition than when present as the monomer in solution, so that the initial effect of pressure tend to compress the micelle and militate against the increased freedom of the monomer in the micelle, thus giving a rise in *cmc*. The decrease in *cmc* may be due to an increase in dielectric constant

of water, making less electrical work necessary to bring a monomer into micelle. Many reports have appeared on the effect of pressure on micelle formation of ionic [45-50] and non-ionic amphiphiles [51]. An increase in *cmc* occurred with increase in pressure approximately upto 105 Mpa, followed by *cmc* decrease at higher pressure. For nonionic amphiphiles, the *cmc* value increases monotonously and then levels off with increasing pressure. La Mesa has also discussed the effect of pressure on the *cmc* [52].

Solvent medium

The polarity of the medium favors surfactant association. Nonpolar medium offers environment similar to the surfactant tail so that their tendency of self-association is reduced. In a good nonpolar medium. *viz.*, cyclohexane, carbon tetrachloride, etc., formation of normal micelle may be totally absent; a reverse orientation (reverse micelle) may occur. In ethylene glycol, the *cmc* of surfactants decreases as the length of the hydrophobic chain increases. But the change is much smaller than in water [53]. For polyoxyethylenated nonionic solutions in benzene and carbon tetrachloride, *cmc* decreases with increase in the length of the polyoxyethylene group at constant hydrophobic chain length.

The *cmc* in benzene for alkylammonium carborxylates increases with increase in the length of alkyl chain of the anion but decrease with increase in the length of the alkyl chain of cation; in carbon tetrachloride, there is no significant change in the value of the *cmc* with these structural changes.

The *cmc* is lower in D_2O than H_2O for different amphiphilies [54,55]. The hydrophobic bonds are expected to be stronger in D_2O than H_2O [56]. Also, micelles in D_2O are larger than H_2O [57].

Types of Micelles

Normal micelle

In 1920 Mc Bain and Salmon proposed the existence of micelles [20]. It was Hartely [58] who made the pioneering contributions to the understanding of the micelles. Hartly micelle is described as having linear chains arranged radially, as in the spokes of a wheel. The structure of normal micelles just above the *cmc* can be considered as roughly spherical [59-62]. When the hydrophobic portion of the surfactant is a hydrocarbon chain, the micelle will consist of liquid-like hydrocarbon core with radius of roughly equal to the fully extended hydrocarbon chain length (~12-30 Å): the polar head groups with the surrounding water are arranged at the micellar surface, which is rough [63]. Menger has proposed that water can penetrate inside the micelle upto a certain level [64, 65]; the idea got support from fluorescence and ^{1}H-NMR measurements. Partial molar volume determinations indicate that the alkyl chains in the core are more expanded than those in the normal liquid state [66].

An ionic normal micelle may contain three regions (Fig. 1.4).

(i) The interior or core of the micelle which is hydrocarbon like as it consists of hydrocarbon chains of the ionic surfactant molecules.

(ii) Surrounding the core is an aqueous layer known as the Stern layer. The Stern layer constitutes the inner part of the electrical double layer. It contains the regularly spaced charged head groups and 60-90% of the counterions (the bound counterions). The head groups are hydrated by a number of water molecules. One or more methylene groups attached to the head group may be wet. The core and the Stern layer form the kinetic micelle.

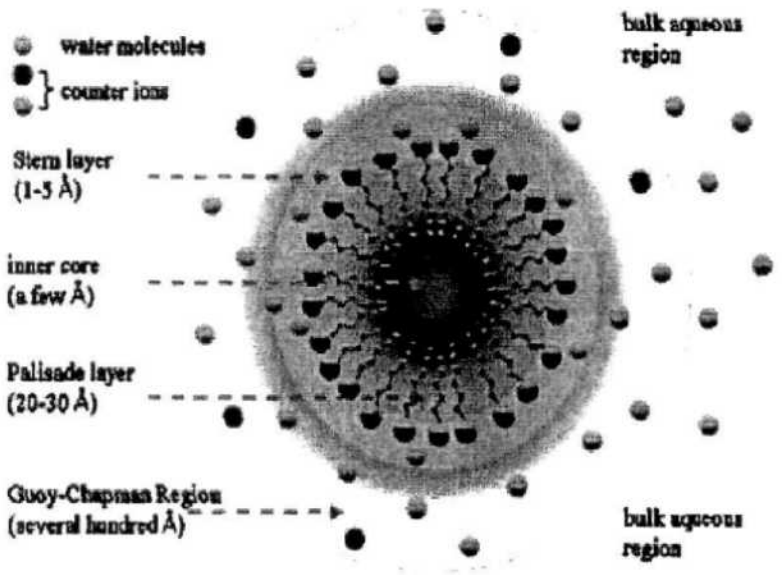


Fig. 1.4: *Schematic representation of the regions of spherical micelle.*

(iii) The outer layer is a diffuse layer and contains the remaining counterions and is called the Gouy-Chapman layer that extends further into aqueous phase. The thickness of this layer is determined by the (effective) ionic strength of the solution.

The head groups and counterions concentrations in the interfacial region of ionic micelle are on the order of 3-5 M, which give the micellar surface some of the properties of the concentrated salt solution [67]. Although the solution as a whole is electrically neutral, both the micellar and aqueous pseudo phase carry a net charge because thermal forces distribute a fraction of the counterions radially into the aqueous phase [28, 68].

For nonionic micelles the structure is essentially the same except that the outer region contains no counterions, but includes coils of hydrated polyoxyethylene chains. Water molecules appear to be trapped on the oxyethylene sites [69].

Reverse micelle

In nonpolar solvents, in the presence of traces of water, surfactants associate to form the so-called reverse/inverted micelles. The structure of micelle is similar to that of normal micelle but inverted. In a reverse micelle, head group of surfactant molecules locate inside to form a polar core and hydrocarbon tails are directed towards the bulk solvent to form the outside shell of the micelle [70-73]. At a very low concentration of surfactant, the reverse micelles are very close to spherical in which water molecules occupy the central part of the sphere, thus forming a so-called micro water-pool, and these water molecules are in contact with head groups of reverse micelle-forming surfactant molecules. The tails of these surfactant molecules are extended toward bulk nonpolar solvent phase (Fig.

1.5). The most often used reverse micellar system is the Aerosol OT (AOT)/H_2O/isooctane system.

In recent years the field of reverse micelles has witnessed a significant growth of interest, partly due to the finding that proteins, other biopolymers, and even bacterial cells can be solubilized in the reverse micellar systems: in fact, this has permitted the extension of the area of interest to new domains, i.e., biocatalysis and chemical biotechnology.

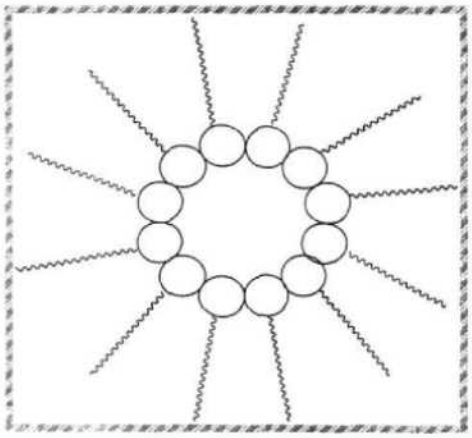


Fig. 1.5: *A two dimensional schematic representation of reverse micelle.*

Mixed micelle

The formation of micelles from more than one chemical species gives rise to what are known as mixed micelles (Fig. 1.6). A mixed micelle is an aggregate of surfactant molecules composed of different types of surfactants present in aqueous solution. Mixed micellar systems are encountered in many applications,

from laundry detergents formulation to industrial and technological systems, due to their better performance characteristics than those consisting of only one type of surfactant [74, 75].

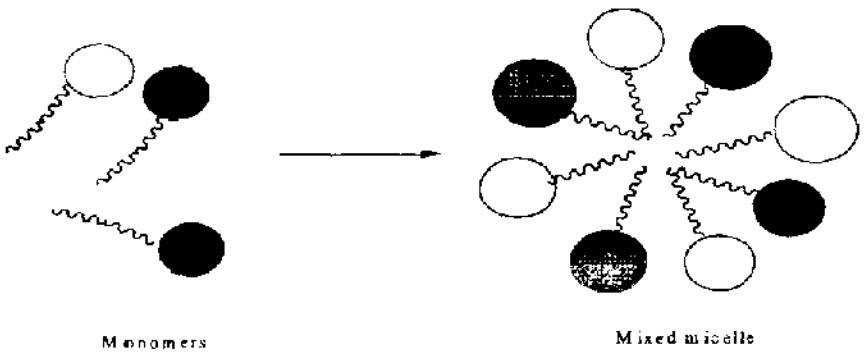


Fig. 1.6: *Schematic representation of formation of mixed micelle by the monomers.*

Mixed micelles are also formed when low molecular weight molecules are solubilized by micelles formed from surfactants containing a relatively larger non-polar side chain. The solubilized substances, also called a penetrating additive [76], may be located in the hydrocarbon core [77], or the hydrophilic mantle [78]. The mixed micellization is a special case of solubilization.

The cmc of the mixed micelles fall within the highest and lowest individual *cmc* values of components [74]. In some cases, two surfactants interact in such a fashion that the *cmc* of the mixture is always intermediate in value between those of two pure components. In other cases, they interact in such a way that the *cmc* of the mixture at some ratio of the two surfactants is less than either of the *cmc*. When this situation arises, the system is said to exhibit synergism, the

condition in which the properties of the mixture are better than those attainable with the individual components by themselves.

Mixed micellar solutions exhibit some very interesting properties not expected from individual surfactant solutions. When an ionic surfactant is mixed with a non-ionic surfactant, the degree of the association falls to zero as mole fraction of non-ionic surfactant in the micelle increases [79, 80]. This is particularly evident for mixtures of anionic and non-ionic surfactants of the polyoxyethylene type, because of the strong interaction between the anionic head group and the ethylene oxide group.

Aggregation Number

An important property of micelle formation is the mean aggregation number which provides direct information about the general size and shape of the aggregates formed by amphiphiles in solutions, and how these properties are related to the molecular structure of the amphiphile. The average number of monomers making up the micelles is know as aggregation number (N) and is typically 30-200 in water. The aggregation number depends on different factors such as the nature of surfactants, temperature [81-83], type and concentration of added electrolytes [84-86], organic additives [87-89], etc.

Many experimental techniques like dynamic light scattering (DLS), small angle neutron scattering (SANS), steady-state fluorescence quenching (SSFQ),

time-resolved fluorescence quenching (TRFG), etc., have been used for determination of the aggregation number [90-97].

Micellar Packing Parameter

The morphology of micellar aggregates is mainly determined by a balance between hydrophobic interactions of the hydrocarbon tails and the electrostatic repulsions and hydration of the head groups [98]. Israelachvili et al. [26] developed a model and defined a packing parameter R_P to predict the aggregate morphology of a given surfactant

$$R_p = V_H / a_o l_c \tag{1.2}$$

In this equation l_c is the chain length of the fully extended all-trans alkyl tail, V_H the volume of the hydrophobic part of the molecule, and a_o the mean cross-sectional head group area. V_H and l_c can easily be calculated from the number of carbons in the chain through the Tanford equation [98]

$$l_c = (1.5 + 1.26\, n)\ \text{Å} \tag{1.3}$$

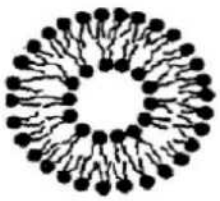
and

$$V_H = (27.4 + 26.9\, n)\ \text{Å}^3 \tag{1.4}$$

where n is the number of carbon atoms of hydrophobic chain embedded in the micellar core. More tricky is the quantification of a_o, especially for cationic and anionic surfactants. The effective size of the head group area depends on the electrolyte and the surfactant concentration. Nagarajan [99] proposed that the

value of a_o possibly also depends on the chain length. The relationships between the effective shape and the packing parameter are related as in Table 1.1

Table 1.1: *Aggregate structures with their corresponding packing parameters.*

Effective shape of the surfactant molecule	Packing parameter (R_p)	Type of aggregation
 cone	<1/3	 spherical micelles
 truncated cone	1/3–1/2	 wormlike micelles
 cylinder	1/2–1	 bilayers
		 Vesicles
 inverted cone	>1	 reverse micelles

Thermodynamic Models of Micelle Formation

The thermodynamics of surfactant systems are of great importance in theoretical and practical purposes, as they affect the stability of ordered micelles *vis-à-vis* disordered free surfactant molecules and/or ions in the solution state. The thermodynamic analysis of micellization has gained wide acceptance through two approaches for application in describing the micelle formation process and thereby allow for the relation of macroscopic equilibrium thermodynamic measurements to molecular processes. They are the pseudo-phase separation model [100-102], which treats micelles as a separate phase formed at and above the *cmc*, and the mass-action model [103-106], which considers surfactant monomers in solution to be in equilibrium with micelles of a fixed size above the *cmc*. An extension of the mass-action model is the multiple equilibrium models [107], which consider the formation of aggregates of various sizes, accounting for the observed polydispersity in aggregation numbers. However, this introduces a large number of variables into any analysis of experimental data making it difficult to apply. The pseudo-phase separation model has been shown to account for, at least semi-quantitatively, the observed concentration dependence of apparent molar properties and has been useful in deriving thermodynamic functions of micellization using both apparent and partial molar properties. The main criticism of this model is that calculated values often show substantial deviation from experimental values for some properties, particularly if the transition from

monomer to micelle formation occurs over a broad concentration range. Nevertheless, because of the simplicity of its application, the pseudo-phase model is widely used to model thermodynamic data, particularly for long-chain surfactants having low *cmc* values. The mass-action model allows for modeling of thermodynamic properties over a broader concentration range, i.e., premicellar range as opposed to the pseudo-phase model which is applicable only in the post-micellar range. Also, prediction of aggregation numbers can be made from the mass-action model, and it has been more successfully applied to short chain surfactants. In both these treatments, the micellization is described in terms of classical system of thermodynamics.

Pseudo-phase separation model

This model considers the formation of micelles to constitute the formation of a separate phase. However, the micelles do not constitute a "phase" according to the true definition of this concept since they are not homogeneous and uniform throughout. An underlying argument for this assumption is that the activity of the monomer surfactant remains constant above the *cmc*, as is seen very often in surface tension measurements by the near constant value of the surface tension. The *cmc* can, therefore, be considered as the solubility limit of the monomeric species. A main criticism to this model is that it predicts that activity of the monomers above the *cmc* remains constant, while dialysis, surface tension and

emf measurements indicate a decrease in monomer activity above the *cmc* of ionic surfactants.

Consider an anionic surfactant, in which n surfactant anions, S^-, and n counterions M^+ associate to form a micelle, i.e.,

$$nS^- + nM^+ \rightleftharpoons S_n$$

The micelle is simply charged aggregate of surfactant ions plus an equivalent number of counter ions in the surrounding atmosphere and is treated as separate phase.

The chemical potential of the surfactant in the micellar state is assumed to be constant, at any given temperature, and this may be adopted as standard chemical potential, μ_m°, by analogy to pure liquid or a pure solid. Considering the equilibrium between micelles and monomers, then,

$$\mu_m^\circ = \mu_1^\circ + RT \ln a_1 \qquad (1.5)$$

where μ_1° is the standard chemical potential of surfactant monomer and a_1 is its activity, which is equal to $f_1 x_1$, where f_1 is the activity coefficient and x_1 the mole fraction. Therefore, the standard free energy of micellization per mole of monomer is given by,

$$\Delta G_m^\circ = \mu_m^\circ - \mu_1^\circ = RT \ln a_1 \cong RT \ln x_1 \qquad (1.6)$$

where f_1 is taken as unity (a reasonable value in very dilute solution). Assuming

the concentration of free surfactant in the presence of micelles to be constant and equal to the cmc value, x_{CMC}, then

$$\Delta G_m^\circ = RT \ln[cmc] \qquad (1.7)$$

In equation (1.7), the *cmc* is expressed as a mole fraction, which is equal to (C/55.5+C), where C is the concentration of surfactant in M, i.e.,

$$\Delta G_m^\circ = RT \ln C - RT \ln(55.5 + C) \qquad (1.8)$$

ΔG_m° should be calculated using *cmc* expressed as a mole fraction as indicated by equation (1.8).

The phase separation model has been questioned for two main reasons. Firstly, according to this model a clear discontinuity in the physical property of a surfactant solution, such as surface tension, turbidity, etc., should be observed at the *cmc*. This is not always found experimentally and the *cmc* is not a sharp break point. Secondly, if two phases actually exist at the *cmc*, then equating the chemical potential of the surfactant molecule in the two phases would imply that the activity of the surfactant in the aqueous phase would be constant above the *cmc*. If this was the case, the surface tension of a surfactant solution should remain constant above the *cmc*. However, careful measurements have shown that the surface tension of a surfactant solution decreases slowly above the *cmc*, particularly when using purified surfactants.

Mass-action model

This model gives more appropriate description of the micellar process. This model predicts micelles and unassociated monomers to be in association-dissociation equilibrium, i. e.,

$$n\mathrm{S} \xleftrightarrow{K_m} \mathrm{S}_n$$

$$\mathrm{K}_m = \frac{[\mathrm{S}_n]}{[\mathrm{S}]^n}$$

where K_m is the equilibrium constant.

The standard free energy per monomer is then given by

$$-\Delta G_m^\circ = -\frac{\Delta G}{n} = \frac{RT}{n} \ln K_m = \frac{RT}{n} \ln[\mathrm{S}_n] - RT \ln[\mathrm{S}] \qquad (1.9)$$

For many micellar systems, $n > 50$ and, therefore, the first term on the right-hand side of equation (1.9) may be neglected, resulting in equation (1.10) for ΔG_m°,

$$\Delta G_m^\circ = RT \ln[\mathrm{S}] = RT \ln[cmc] \qquad (1.10)$$

which is identical to equation (1.7) derived using the phase-separation model.

The mass action model allows a simple extension to be made to the case of ionic surfactants, in which micelles attract a substantial proportion of counter ions into an attached layer. For a micelle made of n-surfactant ions, where $(n\text{-}p)$ charges are associated with counter ions, i.e., having a net charge of p units and

degree of dissociation p/n, the following equilibrium may be established (for an anionic surfactant with Na^+ as counter ions),

$$nS^- + (n-p)Na^+ \overset{K_m}{\rightleftharpoons} S_n^{p-}$$

$$K_m = \frac{[S_n^{p-}]}{[S^-]^n[Na^+]^{(n-p)}} \tag{1.11}$$

Phillips has given a convenient solution for relating ΔG_m° to $[cmc]$, arriving at equation (1.12)

$$\Delta G_m^\circ = [2 - (\frac{p}{n})]RT \ln[cmc] \tag{1.12}$$

For many ionic surfactants, the degree of dissociation p/n is 0.2, so that,

$$\Delta G_m^\circ = 1.8RT \ln[cmc] \tag{1.13}$$

Comparison with equation (1.10) clearly shows that, for similar ΔG_m°, the $[cmc]$ is about two orders of magnitude higher for ionic surfactants than with nonionic surfactants of the same alkyl chain length.

In the presence of excess added electrolyte, with mole fraction x, the free energy of micellization is given by the expression,

$$\Delta G_m^\circ = RT \ln[cmc] + [1 - (\frac{p}{n})] \ln x \tag{1.14}$$

Equation (1.14) shows that as x increases, the $[cmc]$ decreases.

It is clear from equation (1.12) that as p=0, i.e., when most charges are associated with counter ions,

$$\Delta G_m^\circ = 2RT \ln[cmc] \tag{1.15}$$

Whereas, when $p \sim n$, i.e., the counter ions are bound to micelles,

$$\Delta G_m^\circ = RT \ln[cmc] \tag{1.16}$$

which is the same equation as for nonionic surfactants.

Drugs and their Classification

The term drug is derived from the French word "Drogue" which means 'a dry herb'. According to definition of the World Health Organization, a drug is any substance or product that is used to modify or explore physiological systems or pathological states for the benefit of the recipient [108]. In the context of medicine, it means a chemical used in the prevention, diagnosis or treatment of disease.

It is to be noted that drugs are to be used for the benefit of recipient and it is presumed that this refers to total benefit–physical, mental as well as economical. Drugs are regarded as biologically active chemical compounds mostly with a therapeutic purpose which can be broadly classified into:

(i) Biological classification (based on pharmacotherapeutic and chemotherapeutic agents)

(ii) Chemical classification (based on drugs' chemical structure)

(iii) Classification of drugs according to commercial consideration (classified according to operational expenses, research investment, and profit margins)

(iv) Classification by the lay public (classification depending on the action of the drug, like antiseptic, tonics, laxative, etc.).

A wide variety of drugs are, in fact, known to be surface active in nature [109-124]. This activity does not appear to be a fortuitous coincidence. In a number of cases excellent correlations between surface activity and biological effects have been demonstrated.

Many pharmacologically active compounds being amphiphilic, may undergo different kinds of associations and whose site of action in the organism frequently is the plasma membrane. Even if their target is intracellular, the interaction with this first barrier plays a fundamental role [125].

Formation of cell membranes and location of receptor proteins in lipid bilayers is a consequence of surface activity. It is, therefore, logical to expect that the drugs acting by altering the permeability cell membranes after interacting with them are likely to be surface active in nature. This is because the lipid bilayers, with receptors in them, represent the interface and the drugs interacting with them will not reach the interface unless they are surface active in nature.

Surface activity is of ubiquitous presence in living systems. Take any body fluid or cell soup, its surface tension is always less than that of water. Molecules of surface active nature are crucial to living matter and its organization. Formation of biological cell is, as a matter of fact, a consequence of surface activity. Surface activity in living systems is a matter of evolution, i.e., it is need based and therefore should have a crucial role to play in biological action.

Theories of Drug Action

There are three theories relevant to drug action, namely, occupancy theory, rate theory, and inactivation theory.

(i) Occupancy theory

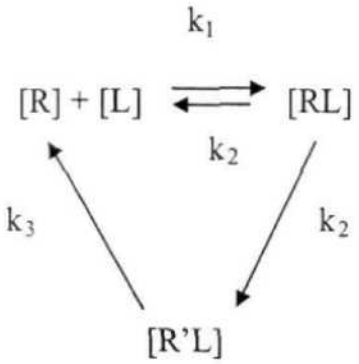
Biological responses to drugs are, as a rule, graded; they can be measured on a continuous scale and, there is a systematic relationship between the dose of a drug and the magnitude of the response. Application of the law of mass-action to the dose-response relationship was largely done by Clark [126,127]. An observed biological effect was assumed to be a reflection of the combination of drug molecules with receptors. The magnitude of a response was postulated to be directly proportional to the occupancy of receptors by drug molecules. The maximal response is assumed to be obtained when all the receptors are occupied.

(ii) Rate theory

The central idea in this theory is different from that in the occupancy theory. Instead of attributing excitation to the occupation of receptors by drug molecules, it is attributed to the process of occupation–each association between a drug molecule and a receptor providing one quantum of excitation. The magnitude of biological response is proportional to the rate at which drug molecules associate with receptor sites. This rate depends on the concentration of free drug, the concentration of free receptor sites and the rate constants for association of drug molecules with receptor [128-130].

(iii) Inactivation theory

Receptor inactivation theory is based on the two state model originally proposed by Katz and Thesleff for ion channels [131]. Kenakinn on his work on the Torpedo nicotinic receptor reported that the multimeric receptor exists in active and inactive states with ligand binding altering the equilibrium between these two states. Receptor inactivation theory reflects a synthesis of both occupancy theory and rate theory providing an alternative consideration for the study of the receptor ligand interaction. Inactivation theory assumes that RL complex is an intermediate "active state" that gives rise to an inactive form of the receptor, R', which is part of an RL complex termed R'L [132]



where R stands for receptor and L for ligand, and k's being corresponding rate constants.

Classes of amphiphilic drugs include analgesics [133], antihistamines [134], local anesthetics [135-140], tricyclic antidepressants [141-145], phenothiazine [146-153] and benzodiazepine [154] tranquillizers [155-158], peptide [159] and non-peptide [160,161] antibiotics [162-164], anticholinergics [165], β-blockers [166], non-steroidal anti-inflammatory drugs [167], anticancer

drugs [168]. Many of these drugs contain one or more (condensed or not) aromatic nuclei, while others are of peptide nature. A great deal of data on the surface active properties of drugs can be found in the book authored by Attwood and Florence [169], and in other reviews [170-172].

Surface active drugs of quite different chemical structure are reported to self-associate and bind to membranes, causing disruption and solubilization, in a surfactant-like manner. Depending on the kind of drug, the self-association of these drugs is classified into two modes: micellar and non-micellar aggregations. Here the micellar aggregation means that a single multimer (micelle) forms above the *cmc*, and non-micellar (stepwise) aggregation means that i-mer is successively formed by aggregation of (i–1)-mer and monomer.

Micellar Solubilzation of Hydrophobic Drugs

An important property of micelles is their ability to increase the solubility of sparingly soluble substances in water. In this context, solubilization can be defined as the spontaneous dissolving of substance by reversible interaction with the micelle of surfactant in water to form a thermodynamically stable isotropic solution with reduced thermodynamic activity of the solubilized material [173]. Micellar system can solubilize poorly soluble drugs and thus increase their bioavailability, they can stay in the body (blood) long enough to provide gradual accumulation in required areas, and their sizes permit them to accumulate in areas with leaky vasculature [174].

The locus of solubilization, i.e., location in the micelle at which solubilization occurs, varies with solubilized material as it reflects the type of interaction between the surfactant and the solubilizate. Solubilization studies were made by different techniques using X- rays diffraction [175], NMR spectrometry [176], UV-visible [177-180], and fluorescence [181]. The diffraction studies give us changes in the dimensions of micelles upon solubilization, whereas UV, NMR, and fluorescence spectra record changes in the environment of solubilizate on solubilization. From such studies, Rosen [182] has stated a number of different sites in the micelle, Fig. 1.7: (1) on the surface of micelle, at the micelle water interface, (2) between hydrophilic head groups, (3) in the palisade layer of the micelle between hydrophilic groups and first few carbon atoms of the hydrophobic groups that comprise the outer core of the micellar interior , and (4) in the inner core of the micelle.

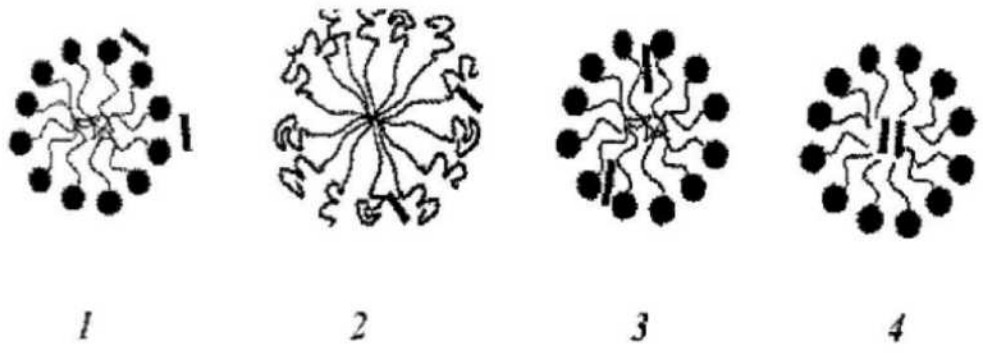


Fig. 1.7: *Possible loci of solubilization of solubilizate in surfactant micelles.*

Accordingly, hydrophilic drugs can be adsorbed on the surface of the micelle (1), drugs with intermediate solubility should be located in intermediate

positions within the micelle, such as between the hydrophilic head groups of PEO micelles (2) and in the palisade layer between the hydrophilic groups and the first few carbon atoms of the hydrophobic group, that is outer core (3) and completely insoluble drugs may be located in the inner core of the micelle (4) [173,174].

The existence of different sites of solubilization in micelle results from the fact that the physical properties, such as microviscosity, polarity and hydration degree, are not uniform along the micelle [183].

The capacity of surfactants in solubilizing drugs depends on numerous factors, such as chemical structure of the surfactants, chemical structure of the drug, temperature, pH, ionic strength, etc. [174]. Solubilization of drugs in micellar solutions has been investigated extensively. Excellent reviews on this topic can be found in the literature [169,184]. The benefits of micellar solution as drug delivery vehicles arise mainly from the solubilization power of surfactants and thus the elimination of dissolution as a rate–limiting step in the process for absorption. They may reduce toxicity caused by administering neat drug and improve the stability of labile drugs.

It is important to improve the solubility for poorly soluble drugs because these drugs possess low absorption and bioavailability [185]. As solubility is an important determinant in drugs liberation, it plays a key role in its bioavailability. Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption [186,187].

The hydrophobic micellar moiety of both nonionic and anionic surfactants solubilizes nonionizable solutes with poor aqueous solubility [188]. The polarity of solute molecules is a major factor in determining the degree of solubilization. It has been observed that the solubilizing capacity of ionic and nonionic surfactants for solutes that are located in the micellar interior increase in the order of anionic < cationic < nonionic. This effect has been attributed to a corresponding increase in the area per head group of the series, leading to "looser" micelles with less dense hydrocarbon cores that can accumulate more solute [189].

Hamza and Kata [190] found that the solubilizing power of polysorbates was directly related to the alkyl chain lengths with an increase in the chain length corresponding to an increase in the solubilizing capacity. Surfactant mixtures are also often employed in drug solubilization since such mixtures exhibit high solubilization potential for hydrophobic drugs [191-193]. They can lead to changes in the size and shapes of micelles, as well as to increase in the amount of solubilizate in surfactant solutions [194].

Relevance of the Research Problem

Many pharmacologically active compounds are amphiphilic or hydrophobic molecules, which undergo different types of association, and whose site of action is frequently the plasma membrane [195]. This membrane affinity is the measure of the hydrophilic- hydrophobic interactions in the molecule and can be related to the surface activity of drugs. Although the pharmacological effect of drug

molecules is usually manifest at low concentrations where self-association is not important, it is likely that accumulation of drug molecule at certain sites in the body may cause a localized high concentration resulting in aggregation and subsequent changes in biological activity due to decreased transport rates or decreased ability to pass through biological barriers [169].

A most common challenge faced by pharmaceutical scientists as well as industry is to design and develop drugs with good aqueous solubility while simultaneously retaining potency and selectivity [196]. The absorption properties (which cause also bioavailability) of these compounds are influenced by their physico-chemical and biological properties. A number of methodologies have been adopted to improve the aqueous solubility (and hence bioavailability) of drugs. This problem can be overpowered by the use of mixed micelles of drug–surfactant or surfactant–surfactant. Drug delivery systems which have attracted much attention for their potential to improve the pharmacological properties of the drug include nanocapsules [197], cell ghost [198], liposomes [199] and micelles [200].

A mixed amphiphile system can exhibit surface and colloidal properties different from those of pure individual components. Nonideal mixing of amphiphilic components often causes synergism in the properties of the mixtures that may be exploited in their applications. As a result, mixed micelles are commonly used in pharmaceutical formulations, in industries, and in enhanced oil recovery processes.

Keeping the above in mind, we have examined the following aspects: (i) mixed micellization study of surfactants with amphiphilic drugs, (ii) solubilization of a hydrophobic drug (Phenytoin) in surfactants.

In order to understand the effect of additives on the association behavior of amphiphilic drugs, we have also determined their *cmc* in presence of various concentrations of additives.

The U.V. spectroscopic technique was used to evaluate the solubilization of Phenytoin in surfactants.

Layout of the Thesis

This thesis consists of the following four chapters:

Chapter-I: General introduction

Chapter-II: Experimental

Chapter-III: Studies of Amphiphilic Drugs in Presence of Surfactants & Salts

This chapter is divided into two parts, i.e.,

(a) Drug–Surfactant Systems

(I) Studies with cationic surfactants

(II) Studies with anionic surfactants

(III) Studies with nonionic surfactants

(b) Drug–Salt Systems

Chapter-IV: Solubilization of Phenytoin (PHT) by Cationic Gemini Surfactants (16-s-16 and 14-s-14, s = 4,5,6) and the Binary Mixtures with Nonionic Surfactants

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Chapter-II

Experimental

Materials

All the chemicals used throughout the whole study are listed in Table 2.1. The Table also includes their abbreviated names, structural formulas, sources, and purities.

Preparation of solutions

The water used to prepare solutions was distilled twice over alkaline $KMnO_4$ in all-glass (Pyrex) distillation setup. Specific conductivity of the double distilled water was in range (1-2) x 10^{-6} S cm^{-1}. Special care was observed for cleaning the glass wares with chromic acid, then with water, and finally by rinsing with double-distilled water. Hygroscopic drugs (NOT, CLP) were stored in desiccators. ADP was kept in a refrigerator (at 4 °C). NOT also photosensitive, so it was stored in desiccators at a dark place (wrapped in aluminum foil).

Instrumentation

Surface tension measurements

The surface tension (γ) of the aqueous surfactant solution was measured by a du Noüy tensiometer (Hardson & Co.. Kolkata) at ~ 30 °C temperature using a platinum ring. The tensiometer was calibrated against water. In an experimental run, the γ at each mole fraction was measured by successive addition of concentrated solution of the mixture in pure water at 30°C and the surface tension was measured after proper and thorough mixing and equilibration.

In order to determine the values of critical micelle concentration (*cmc*), two linear fits were used for each of the isotherms. The first line was fitted to the interval of concentration characterized by linear decrease of the surface tension and the second one to the region of concentration with nearly constant surface tension. The *cmc* values were obtained from the break point of the surface tension vs log C curve. The accuracy on the individual surface tension reading is approximately 0.5 mNm^{-1}.

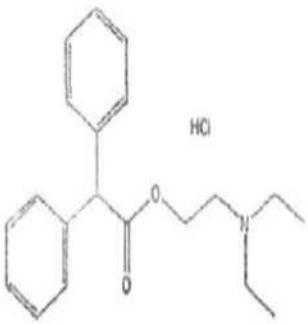
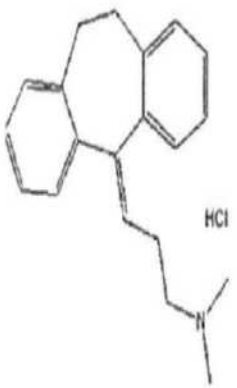
Spectrophotometric measurements

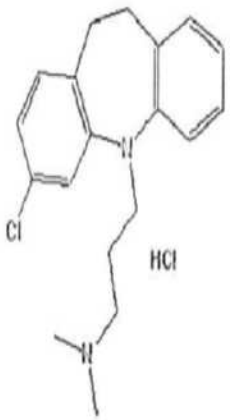
The solubility of PHT was measured in different surfactant solutions with varying concentrations. Excess amounts of PHT were added to vials containing 3 mL of the surfactant solutions to ensure maximum solubility. The sample vials having 5 mL capacity were sealed with screw caps fitted with Teflon-lined septa to prevent any loss. These samples were then agitated with magnetic pieces for a period of 48 h on a magnetic stirrer at a temperature of 30 (±0.5 °C). The solutions were subjected to centrifugation at 15000 rpm to remove the undissolved PHT. The concentration of solubilized PHT was determined spectrophotometrically with a Shimadzu spectrophotometer (Model UV-1650) following appropriate dilution of an aliquot of the supernatant with the corresponding surfactant concentration. The surfactant concentration was kept the same in both the reference and the measurement cells to eliminate the effect of surfactant on UV-absorbance. The solubility of PHT at each surfactant concentration was determined at 215 nm.

^{1}H NMR measurements

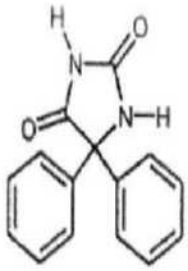
^{1}H NMR spectra of the synthesized geminis were recorded on 300 MHz Bruker Cryomagnet spectrometer (Central Drug Research Institute, Lucknow) in case of 16-s-16, (s = 4, 5, 6) and 400 MHz Bruker Avance II 400 NMR spectrometer (Sophisticated Analytical Instrumentation Facility, Panjab University, Chandigarh) in case of 14-s-14, (s = 4,5,6) in $CDCl_3$ with ^{1}H chemical shifts relative to internal TMS.

Table 2.1: *Name and structural formulas of the chemicals used.*

Name	Abbreviation	Structure/Formula	Make	% Purity
(a) Amphiphilic Drugs:				
Adiphenine hydrochloride ($pK_a = 7.92$)[1]	ADP		Sigma (USA)	99
Nortriptyline hydrochloride ($pK_a = 9.4$)[2]	NOT		Sigma (USA)	= 98

Clomipramin hydrochloride ($pK_a = 9.4$)[2]	CLP		Sigma (USA)	= 98

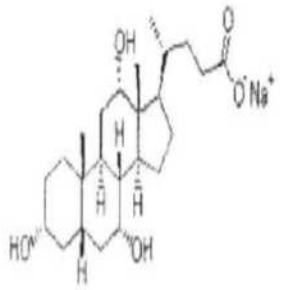
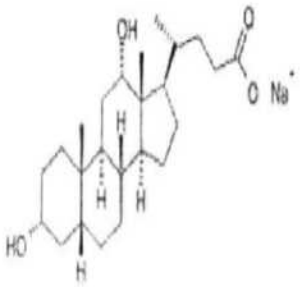
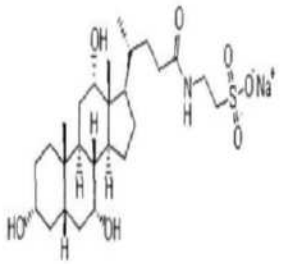
(b) Hydrophobic Drug:

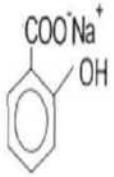
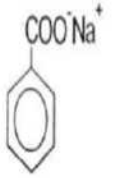
Phenytoin ($pK_a = 8.3$)[3]	PHT		Sigma (USA)	= 99

(c) Surfactants:

1, 4-Bis(*N*-hexadecyl-*N*, *N*-dimethylammonium) butane dibromide	16-4-16	$C_{16}H_{33}(CH_3)_2N^+(CH_2)_4N^+-(CH_3)_2C_{16}H_{33}\ 2Br^-$	Self-synthesized
1, 5-Bis(*N*-hexadecyl-*N*, *N*-dimethylammonium) pentane dibromide	16-5-16	$C_{16}H_{33}(CH_3)_2N^+(CH_2)_5N^+-(CH_3)_2C_{16}H_{33}\ 2Br^-$	Self-synthesized

1, 6-Bis(*N*-hexadecyl-*N*, *N*-dimethylammonium) hexane dibromide	16-6-16	$C_{16}H_{33}(CH_3)_2N^+(CH_2)_6N^+-(CH_3)_2C_{16}H_{33}\ 2Br^-$	Self-synthesized	
1, 4-Bis(*N*-tetradecyl-*N*, *N*-dimethylammonium) butane dibromide	14-4-14	$C_{14}H_{29}(CH_3)_2N^+(CH_2)_4N^+-(CH_3)_2C_{14}H_{29}\ 2Br^-$	Self-synthesized	
1, 5-Bis(*N*-tetradecyl-*N*, *N*-dimethylammonium) butane dibromide	14-5-14	$C_{14}H_{29}(CH_3)_2N^+(CH_2)_5N^+-(CH_3)_2C_{14}H_{29}\ 2Br^-$	Self-synthesized	
1, 6-Bis(*N*-tetradecyl-*N*, *N*-dimethylammonium) hexane dibromide	14-6-14	$C_{14}H_{29}(CH_3)_2N^+(CH_2)_6N^+-(CH_3)_2C_{14}H_{29}\ 2Br^-$	Self-synthesized	
Tetradecyltrimethylammonim bromide	TTAB	$CH_3(CH_2)_{13}N^+(CH_3)_3Br^-$	Sigma (USA)	> 99
Cetyltrimethylammonium bromide	CTAB	$CH_3(CH_2)_{15}N^+(CH_3)_3Br^-$	Merck (Germany)	> 99

Sodium cholate	NaC		Sigma (USA)	= 97
Sodium deoxycholate	NaDC		Sigma (Germany)	= 97
Sodium taruocholate	NaTC		Sigma (USA)	= 97
Polyoxyethylene sorbitan monopalmitate	Tween 40 (T40)		Koch -Light (England)	
Polyoxyethylene sorbitan monooleate	Tween 80 (T80)		LOBA Chemie (India)	

Synperonic	P85		Sigma (Germany)	
synperonic	F108		Fluka (Germany)	
Sodium salicylate	NaSal		Merck (India)	99.5
Sodium benzoate	NaBenz		Merck (Germany)	99.5
Sodium tosylate	NaTos		Fluka (Switzerland)	70-80

(d) Electrolytes:

Sodium chloride	NaCl	—	BDH (England)	≥ 99.9

Sodium bromide	NaBr	—		LOBA Chemie (India)	≥ 99
Potassium chloride	KCl	—		BDH (India)	≥ 99.8
Potassium bromide	KBr	—		Merck (India)	≥ 99

[1] *Hagers Handbuch der pharmazeutischen Praxis*, M. Albinus (Ed.), Berlin (1999).

[2] B. G. Katzung, *Basic and Clinical Pharmacology*, 9th ed., McGraw Hill, New York (2004).

[3] S. P. Agarwal and M. I. Blake, *J. Pharm. Sci.*, **57**, 1434 (1968).

Synthesis of gemini surfactants

There are two main factors which are important in their preparation: one is synthesis and other is purification. The bis(quaternary ammonium) surfactants were synthesized by adopting the following scheme and the procedure outlined in reference [1].

A 1:2.1 equivalent mixture of corresponding α,ω-dibromoalkane with *N*, *N*-dimethylalkylamine in dry ethanol was refluxed (at 80 °C) for 48h. The progress of reaction was monitored using TLC technique. At the end, the solvent was removed under vaccum from the reaction mixture and the solid thus obtained was recrystallized several times from hexane/ethyl acetate mixture to obtain the compound in pure form. The overall yield of the surfactants ranged from 70-90%.

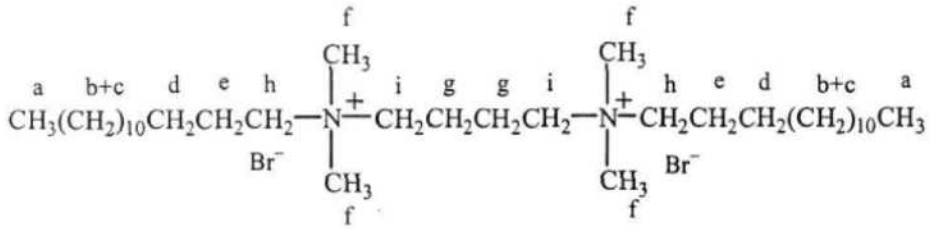
$$Br\,(CH_2)_S\,Br + 2C_nH_{2n+1}N(CH_3)_2 \xrightarrow[48\ h,\ 80\ ^\circ C]{\text{Reflux, dry ethanol}}$$

$$C_nH_{2n+1}(CH_3)_2N^+-(CH_2)_S-N^+(CH_3)_2C_nH_{2n+1}.\ 2Br^-$$

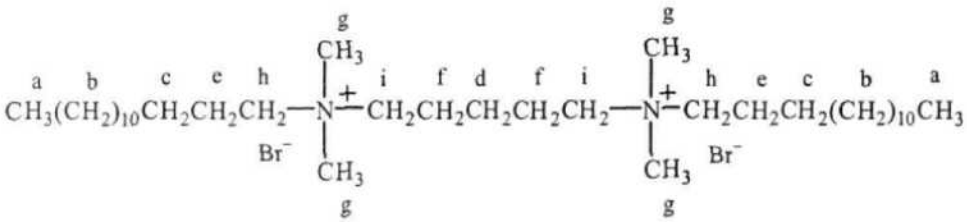
$$(s = 4, 5, 6)$$

The surfactants were characterized by ^1H NMR and cmc determination. Pertinent details are given below.

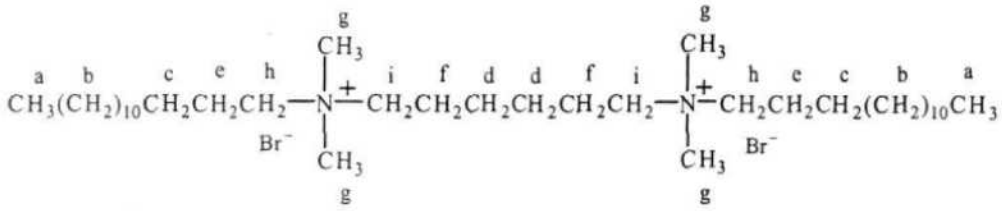
(1) 1, 4-bis(*N*-tetradecyl-*N*, *N*-dimethylammonium)butane dibromide (14-4-14) (Fig.2.1)



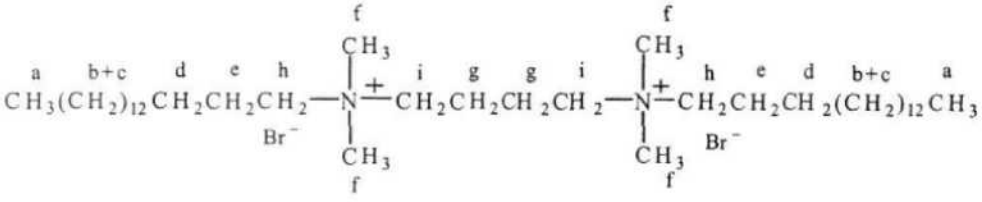
(2) 1, 5-bis(*N*-tetradecyl-*N*, *N*-dimethylammonium)pentane dibromide (14-5-14) (Fig.2.2)



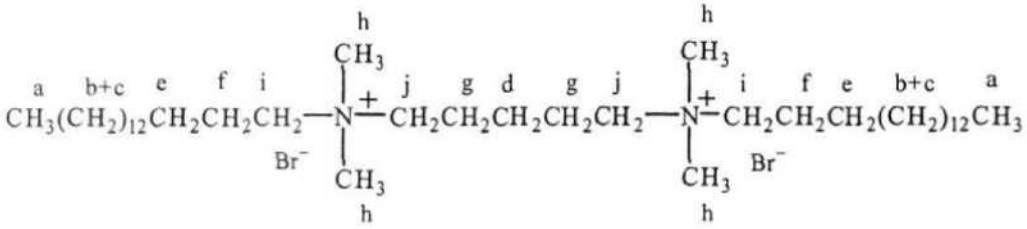
(3) 1, 6-bis(*N*-tetradecyl-*N*, *N*-dimethylammonium)hexane dibromide (14-6-14) (Fig.2.3)



(4) 1, 4-bis(*N*-hexadecyl-*N*, *N*-dimethylammonium)butane dibromide (16-4-16) (Fig.2.4)

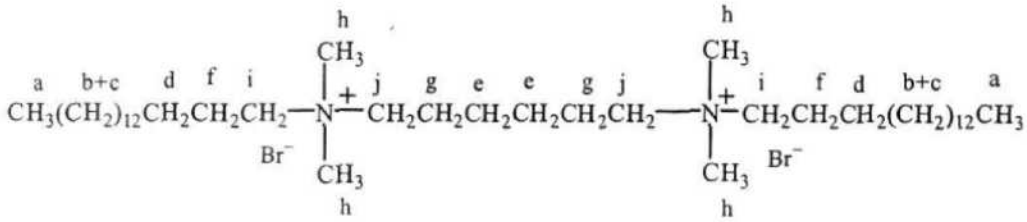


(5) 1, 5-bis(*N*-hexadecyl-*N*, *N*-dimethylammonium)pentane dibromide (16-5-16) (Fig.2.5)



(6) 1, 6-bis(*N*-hexadecyl-*N*, *N*-dimethylammonium)hexane dibromide (16-6-16)

(Fig.2.6)



The ^{1}H NMR data for the indicated groups a, b, c, d, etc., are given in Table 2.2.

Table 2.2: *^{1}H NMR data for m-s-m gemini surfactants.*

Surfactant	Group	δ(ppm)	Number of Protons
14-4-14	a	0.864-0.878	6
	b+c	1.255-1.351	40
	d	1.752	4
	e	2.068	4
	f	3.311	12
	g	3.419-3.461	4
	h	3.613	4
	i	3.789	4
14-5-14	a	0.863-0.897	6
	b	1.355-2.556	40
	c	1.582-1.615	4
	d	1.733	2
	e	2.037-2.074	4
	f	2.953	4
	g	3.387	12
	h	3.512-3.554	4
	i	3.813-3.853	4
14-6-14	a	0.863-0.897	6
	b+c	1.254-1.353	44
	d	1.557	4
	e	1.724	4
	f	1.973	4
	g	2.844	12
	h	3.396	4
	i	3.509-3.711	4

contd...

16-4-16	a	0.883	6
	b+c	1.257-1.344	48
	d	1.754	4
	e	2.084	4
	f	3.308	12
	g+h	3.431	8
	i	1.000	4
6-5-16	a	0.858	6
	b+c	1.257	48
	d	1.617-1.663	2
	e	1.728	4
	f	1.854	4
	g	2.073-2.126	4
	h	3.349	12
	i	3.445-3.501	4
	j	3.853-3.909	4
16-6-16	a	0.857-0.900	6
	b+c	1.255-1.350	48
	d	1.580-1.618	4
	e	1.715	4
	f	1.995	4
	g	2.252	4
	h	3.113	12
	i	3.284-3.712	4
	j	3.903	4

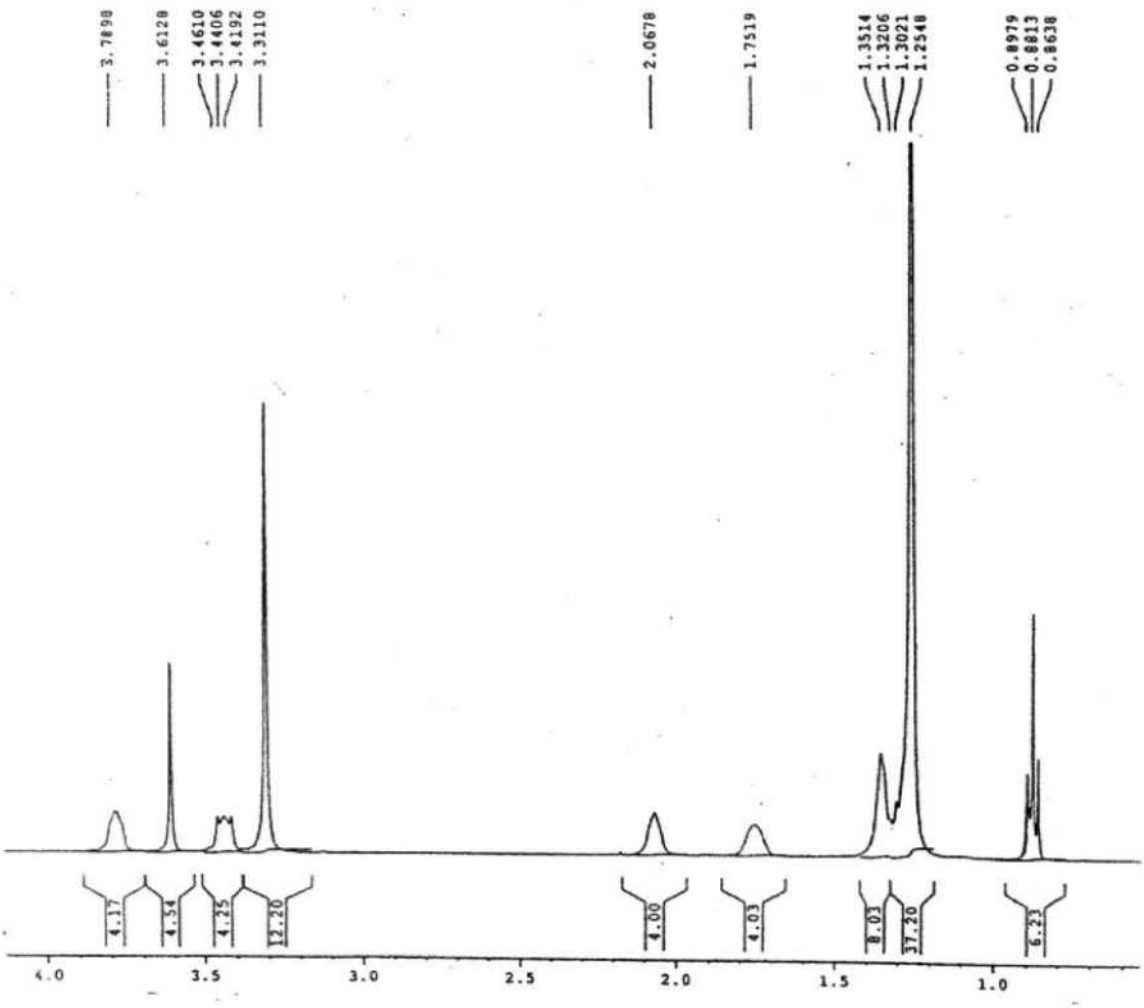


Fig. 2.1: *^1H NMR spectrum of 14-4-14 in $CDCl_3$.*

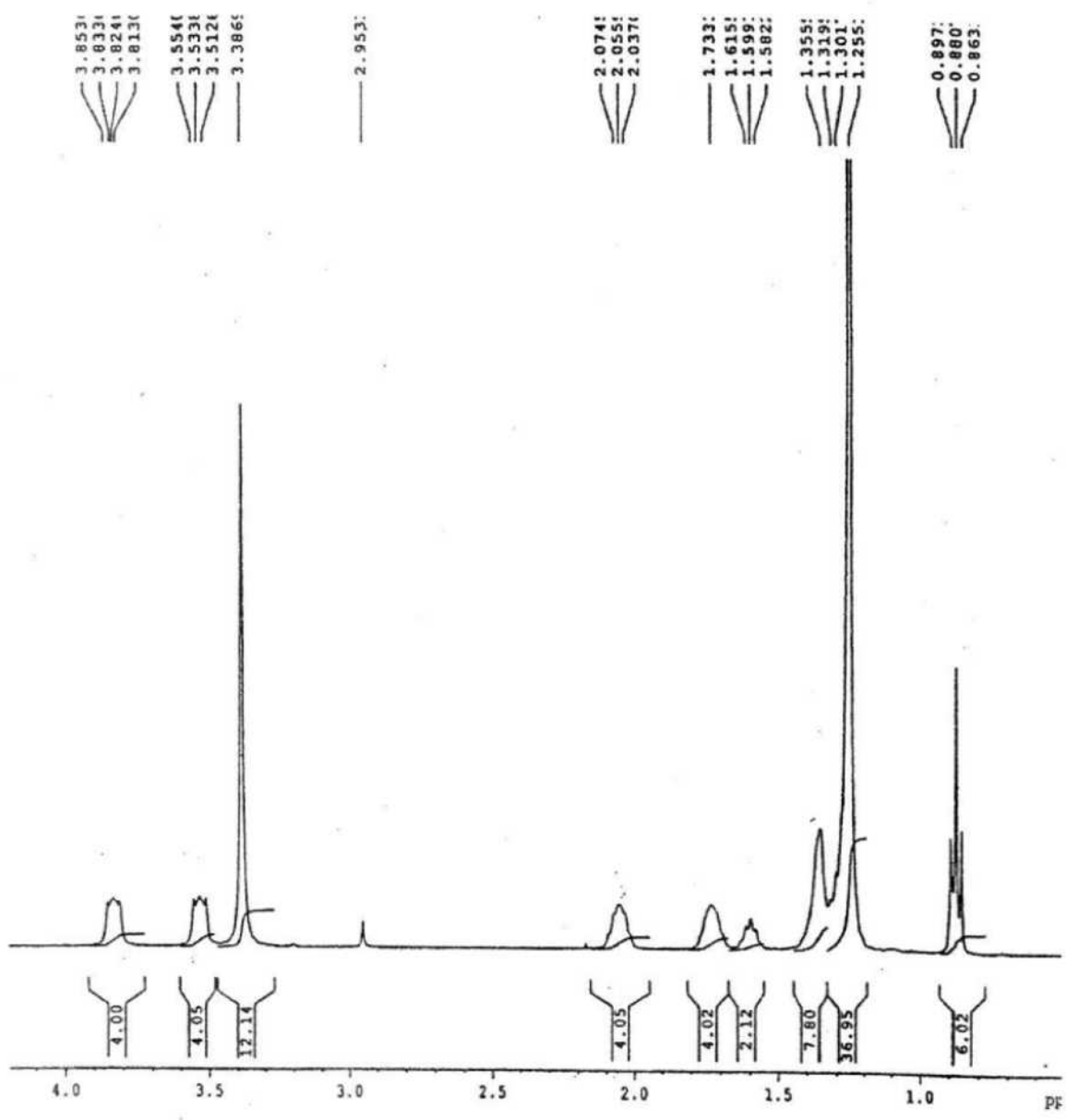


Fig. 2.2: *^1H NMR spectrum of 14-5-14 in $CDCl_3$.*

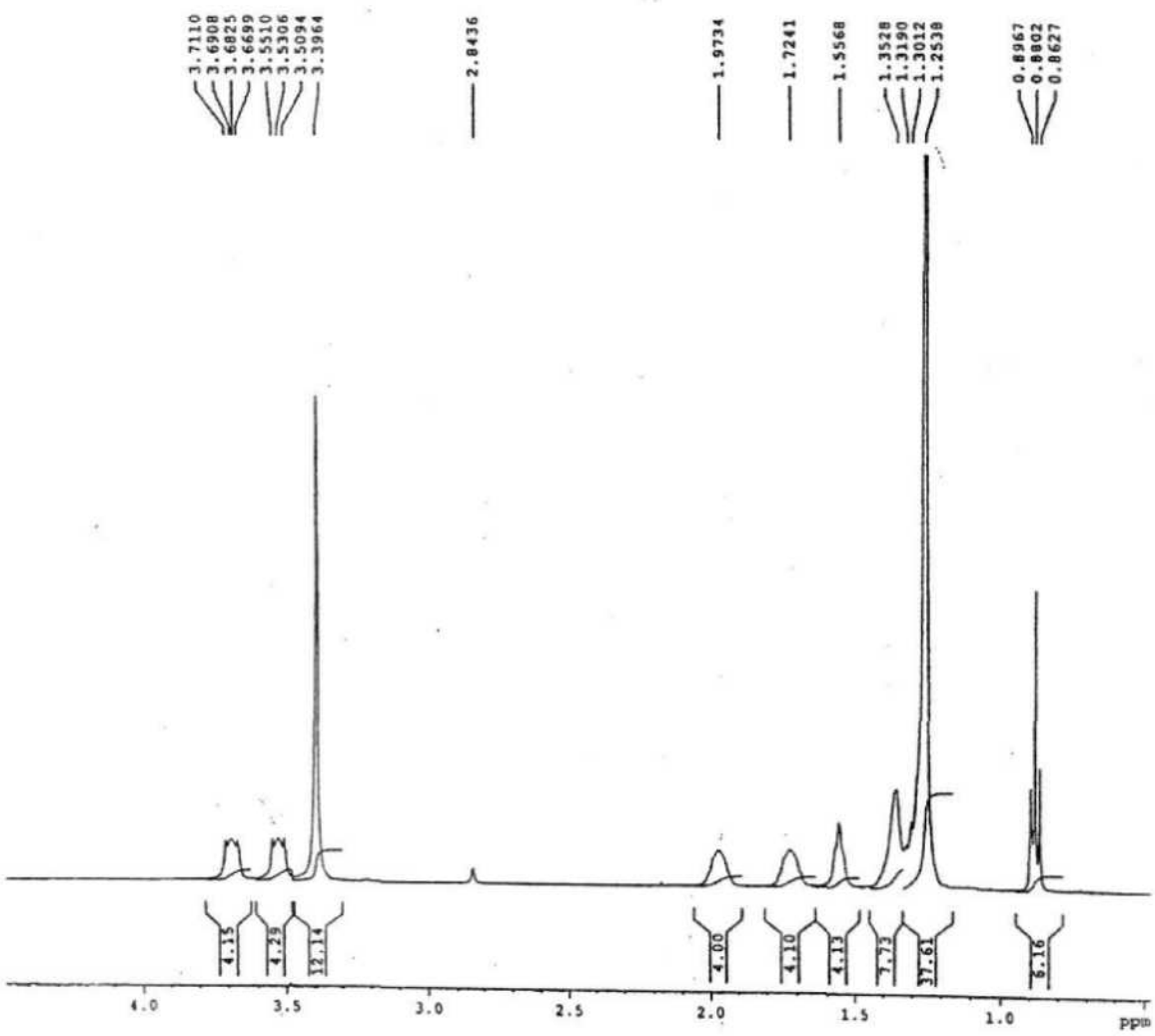


Fig. 2.3: *^{1}H NMR spectrum of 14-6-14 in $CDCl_3$.*

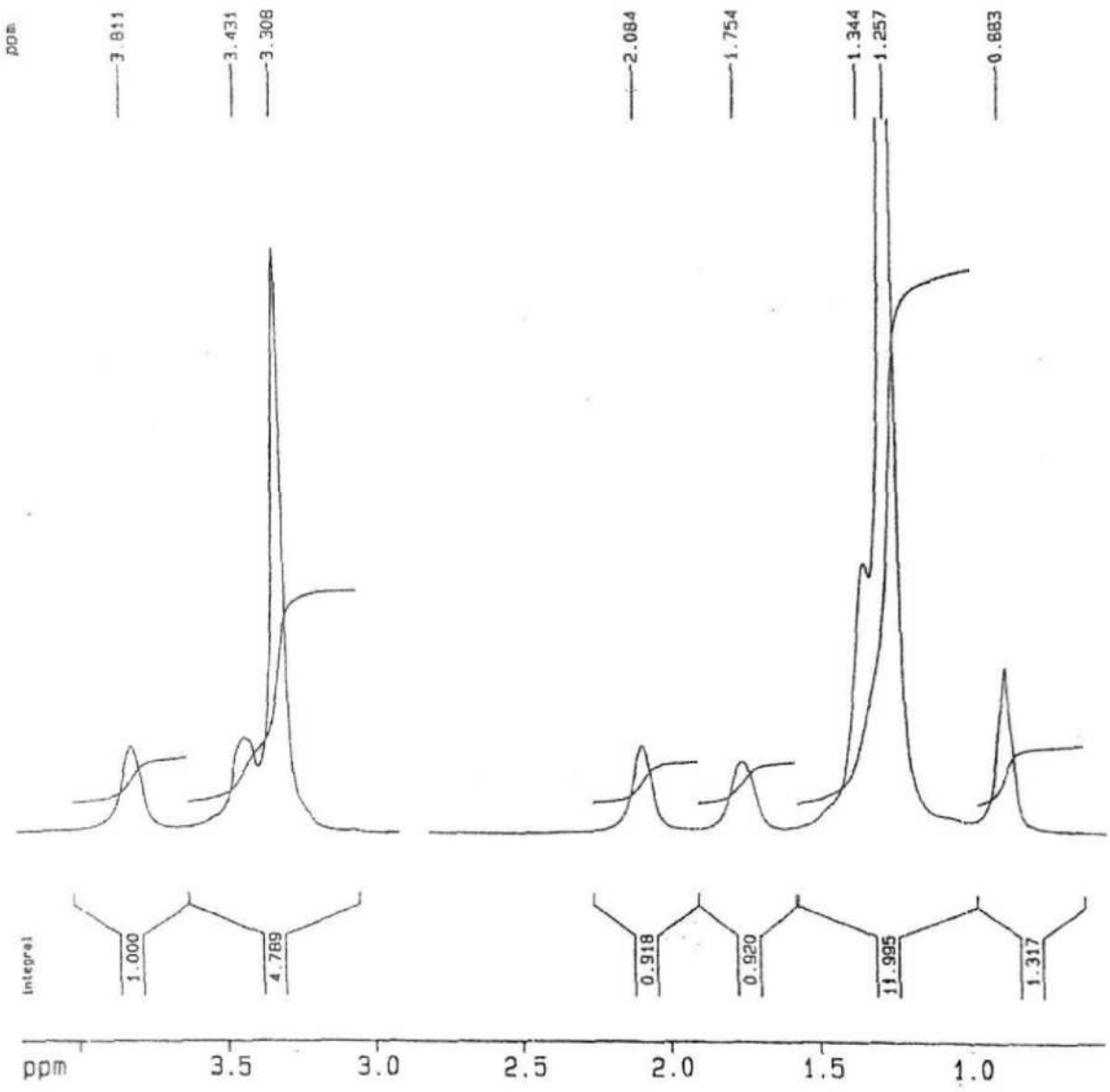


Fig. 2.4: *^1H NMR spectrum of 16-4-16 in $CDCl_3$.*

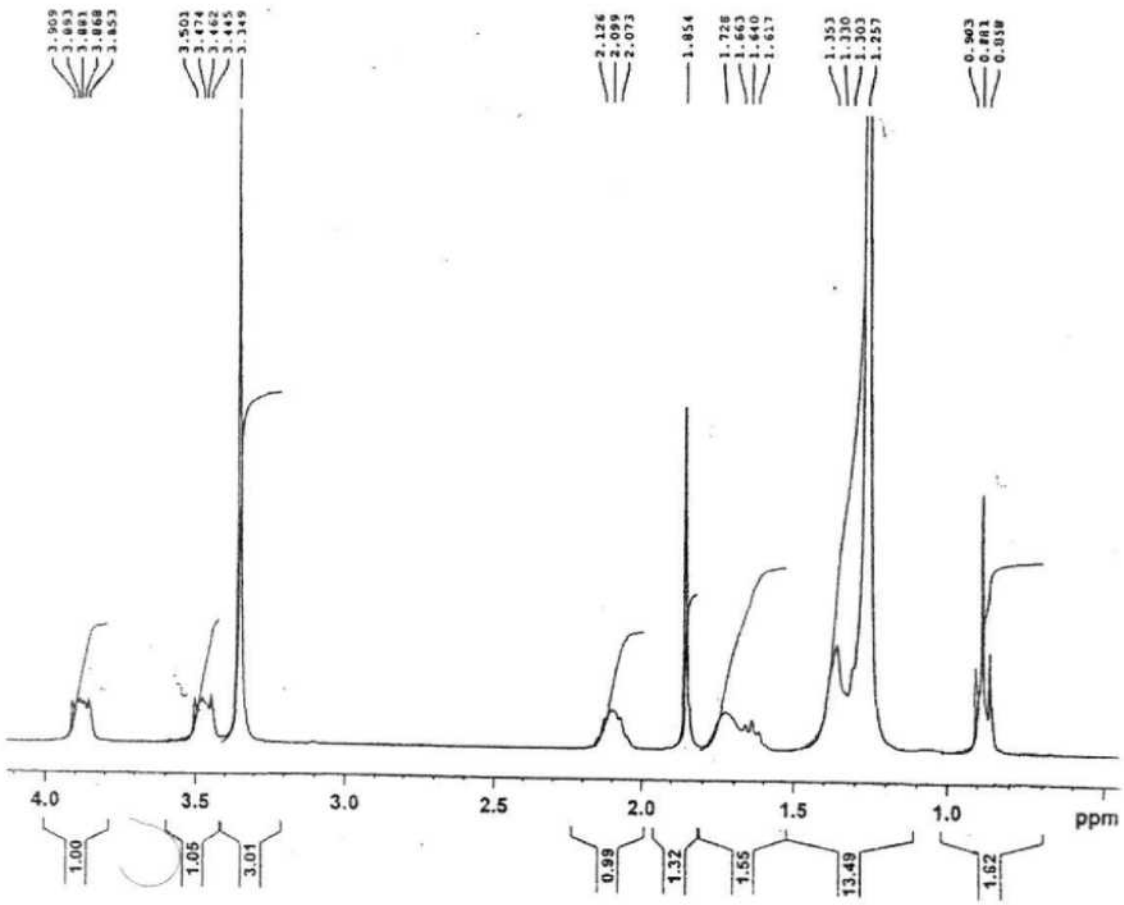


Fig. 2.5: *^1H NMR spectrum of 16-5-16 in $CDCl_3$.*

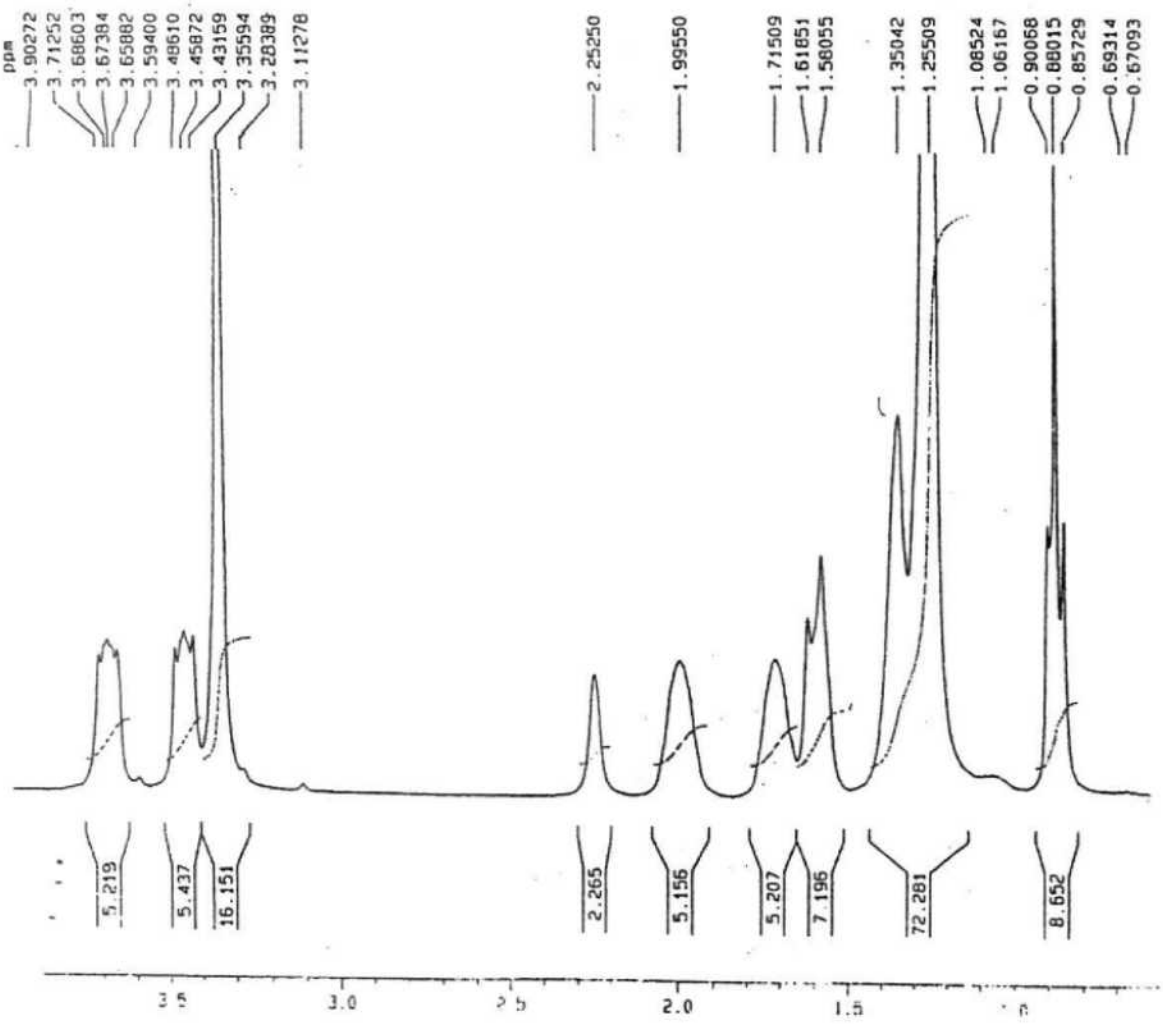


Fig. 2.6: *^1H NMR spectrum of 16-6-16 in $CDCl_3$.*

Reference:

[1] R. Zana, *Adv. Colloid Interface Sci.*, **97**, 203 (2002).

Chapter-III

Studies of Amphiphilic Drugs in Presence of Surfactants & Salts

(A) Drug – Surfactant Systems

(I) Studies with Cationic Surfactants

Introduction

Amphiphilic systems have generated a great deal of interest mainly due to their wide-spread applications in diverse fields. The functions and properties of amphiphiles are interesting because they form various types of assemblies depending on their concentration and environmental conditions such as pH, temperature, type and concentration of additives [1,2].

When an amphiphile is dissolved in water, it disrupts the interaction among the water molecules distorting the water structure. This results in an increase in free energy of the system. This can be overcome by the association of the amphiphiles into micelles. Micellization can, thus, be considered as an alternate mechanism to adsorption at the interfaces. The energetics of adsorption and micellization are usually discussed in terms of various forces operating among the amphiphiles and with the solvent molecules, like attractive forces between the hydrophobic parts, dispersion, van der Waals and electrostatic interactions between the head groups and hydrophobic interactions among the amphiphiles and water molecules. All these factors can be changed with the change in type and structure of amphiphiles which eventually affects the process of micellization as well as of adsorption.

In this respect gemini surfactants are worth mentioning. As compared to conventional surfactants, gemini surfactants are made up of two (or more) amphiphilic molecules joined at the level of head groups by a spacer [3]. These surfactants have10 to 100 times lower critical micelle concentration (*cmc*) than the conventional homologs. It is known that the spacer chain length largely

affects the surface and solution properties of these surfactants [4]. Due to their high molecular weight, their skin penetration is expected to be low. Some cationic gemini surfactants, besides their surface activity, also show antibacterial properties [5,6]. In addition to this, as the gemini surfactants have been found more efficient than their conventional single chain counter part in their interaction with serum albumin [7], they may be used more effectively in the renaturation of proteins produced in genetically engineered cells via the artificial chaperone protocol.

One major problem of pharmacology is that no drug produces a single effect. The primary effect is the desired therapeutic effect. Secondary are all other effects beside the desired effect which may be either beneficial or harmful. Generally, a concentration higher than the amount required for therapeutic effect is present in formulations. If too high a concentration is used, the side effects would be more. Use of drug with a carrier reduces these harmful effects. The most commonly used carriers are polymers, liposomes, niosomes, micelles and lipoproteins. Micelles have an advantage as they are easy to prepare, have long shelf-life and reduce the amount of both drug and carrier, making them cost effective and less toxic [8,9]. As conventional surfactants have higher *cmc* values than geminis, micelles of conventional surfactants may disintegrate upon introduction in large blood volume. Hence, geminis provide a better option as drug carrier. Towards finding new and/or improved applications, a way of changing the properties of an amphiphile is to mix it with a surface active compound so that synergism can take place. A

mixed amphiphile system thus formed can exhibit surface and colloidal properties different from those of the pure individual components. The effectiveness of mixed systems is related to interactions among different components which can increase or decrease the synergism in the system. The magnitude and nature of these interactions as well as the composition of mixed monolayers and mixed micelles can be determined employing different models [1,10-16]. Synergism in the properties of binary mixtures that may be exploited in their application in industrial preparations and pharmaceutical formulations may be due to non-ideality of mixing in binary mixtures of amphiphilic compounds [17].

Adiphenine hydrochloride (ADP) is an anticholinergic which is used to treat Parkinson's disease, gastrointestinal and respiratory disorder. Its use may, however, result in increased heart rate and, if taken in significant amount, a toxic reaction may take place in the body. Nortriptyline hydrochloride (NOT) and clomipramine hydrochloride (CLP) are tricyclic antidepressants. These drugs are used for the treatment of major depression. Hence, these drugs should be used with a carrier in order to reduce the side effects. Keeping all these facts in mind, we have performed tensiometric measurements on ADP, NOT and CLP–cationic surfactant mixtures. Various parameters are evaluated using Clint's, Rubingh's and Motomura's approaches. Adsorption behavior of mixed monolayers was also studied using Gibb's equation. The surfactants used are the so-called alkanediyl–α,ω–bis(dimethylalkylammonium bromide), m-s-m type cationic geminis with m = 14 or 16 and s = 4, 5, 6 and their monomeric

counterparts, i.e., tetradecyltrimethylammonium bromide (TTAB) and cetyltrimethylammonium bromide (CTAB) and the drugs used are ADP, NOT and CLP.

Results and Discussion

Mixed micellization of drug-cationic surfactants

Table 3.1 records the *cmc* values of pure components and the effect of mole fraction of the added surfactants (α_1) on the *cmc* of drug–surfactant mixtures (evaluated on the basis of tensiometric measurements, Figs. 3.1 to 3.9). The *cmc* of pure surfactants agree well with literature [18,19,20].

Also the values of *cmc* of pure drugs obtained in this work are in accordance to those reported in literature [21] except for ADP. The value of *cmc* for ADP is lower than values determined from light scattering (LS) measurements. This may be due to the difference in techniques used. Literature also contains similar results of lower tensiometric values than LS values [22,23]. The *cmc* values of drugs follow the order: ADP > CLP ≈ NOT. The tail part of ADP is short (hence less hydrophobic) and the head part is very rigid. Both these factors decrease the tendency of ADP to micellize. NOT and CLP are structurally similar and difference in their *cmc* values is due to the attached substituents. All the drugs have Cl^- ion as counterion. The lone-pair of electrons on the ring nitrogen of CLP undergoes resonance with the aromatic rings. This results in tautomers with zwitterionic character which decreases the hydrophobicity of the drug. However, presence of a Cl atom at R_2 position and an extra CH_3 group in CLP (as compared to NOT) increases the hydrophobicity

of the drug. Hence, the overall hydrophobicity of CLP comes out to be almost equal to that of NOT and the *cmc* values of the two drugs are almost equal. At the mole fractions studied, *cmc* decreases with the addition of conventional as well as gemini surfactants, this suggests that the mixed micelles are formed in the solution and the surfactants are penetrating into the micelles formed by the drug molecules. As gemini surfactants contain two hydrophobic chains, they increase hydrophobic interactions and enhance the tendency of drugs to form micelles to a larger extent than the conventional surfactants. The *cmc* values of the mixed systems usually fall in between the values of pure components. Also in our systems the values of *cmc* of drug-surfactant mixtures are in between the pure components. This means that the mixed micelles are formed due to attractive interactions among the two components.

The ideal-nonideal behavior of mixed systems can be examined by Clint's model [10].

$$\frac{1}{cmc^*} = \sum_{i=1}^{n} \left(\frac{\alpha_i}{cmc_i} \right) \tag{3.1}$$

Here α_i and cmc_i are the mole fraction and *cmc* of i^{th} component. The *cmc** values decrease with the mole fraction of the surfactants in the solution. As the mole fraction of surfactants in the solution is low the *cmc** values remain close to the *cmc* of pure drug. The *cmc** values are greater than *cmc* value. The difference between the two values gives the extent of non-ideality in the system. Lower *cmc* values indicate that the mixed micelles are formed through attractive interactions.

Nonideal behavior can be quantitatively understood by Rubingh's model [11]. Rubingh's model is an optimization algorithm toward the *cmc* of mixed system from the *cmc* of pure components. Their mole fractions and interaction parameters are optimization parameters. This model considers mixed micelles as a regular solution. The equations are as

$$\frac{(X_1^m)^2 \ln[(cmc\alpha_1 / X_1^m\, cmc_1]}{(1-X_1^m)^2 \ln[(1-\alpha_1)\, cmc/(1-X_1^m)cmc_2]} = 1 \qquad (3.2)$$

and

$$\beta^m = \frac{\ln[(\alpha_1 cmc)/(X_1^m\, cmc_1)]}{(1-X_1^m)^2} \qquad (3.3)$$

The values of X_1^m (Tables 3.2 to 3.4) increases with the increase in surfactant content. With the increase in spacer chain X_1^m decreases marginally.

The X_1^m values show that both drug and surfactants have equal contribution in mixed micelle formation. This shows that the surfactants are more hydrophobic than the drugs and the micelle formation is more spontaneous for surfactants.

The mixed micelle formation, due to the attractive and repulsive interactions, are indicated by negative and positive β^m values, respectively, while a value close to zero refers to an ideal behavior [24].

The negative values of β^m means that the attractive interaction between drug and surfactant is stronger than the individual components.

Mole fraction of surfactants in mixed micelles at ideal mixing conditions, X_1^{id}, is given by

$$X_1^{id} = \frac{\alpha_1 cmc_2}{\alpha_1 cmc_2 + \alpha_2 cmc_1} \qquad (3.4)$$

X_1^{id} values increase with the concentration of surfactants and decrease with the spacer length's increase. Both X_1^m and X_1^{id} are lower for 14-s-14 series as compared to 16-s-16, which is understood by the fact that 14-s-14 series surfactants are less hydrophobic than 16-s-16. Nonideality in the mixed micelles can be explained by deviation of X_1^m from the corresponding X_1^{id} values. Tables 3.2 to 3.4 show the variation of X_1^m and X_1^{id}. Lower X_1^m values than the corresponding X_1^{id} indicate that the mixed micelles are rich in drug, while higher X_1^m than corresponding X_1^{id} indicate that mixed micelles are rich in surfactant and X_1^m values close to X_1^{id} indicate ideal mixing.

The values of activity coefficients, f_1^m and f_2^m were calculated by equations (3.5) and (3.6) and are given in Tables 3.2 to 3.4

$$f_1^m = exp\{\beta^m (1-X_1^m)^2\} \qquad (3.5)$$

$$f_2^m = exp\{\beta^m (X_1^m)^2\} \qquad (3.6)$$

All the values are less than unity indicating non-ideality in the mixed systems. These values were used to calculated excess Gibb's energy of micellization, ΔG_{ex}°, by the relation [9]

$$\Delta G_{ex}^{\circ} = RT[X_1^m \ln f_1^m + (1-X_1^m)\ln f_2^m] \qquad (3.7)$$

The excess Gibbs energy is a measure of the interactions between the two components in mixed micelles with reference to the interactions between

molecules in micelles formed from respective surfactants. The ΔG_{ex}^{o}, values (Tables 3.2 to 3.4) come out to be negative and the magnitude increases with increase in surfactant concentration, suggesting that the mixed micelles are more stable than the micelles of pure components.

The standard Gibb's energy of micellization ΔG_m^o of the pure and mixed systems was calculated using the relation:

$$\Delta G_m^o = RT \ln X_{cmc} \tag{3.8}$$

where X_{cmc} is the *cmc* expressed in mole fraction units. The values of ΔG_m^o, given in Tables 3.2 to 3.4, are negative and their magnitude increases with the mole fraction of surfactants. As is clear from *cmc* values and structure of drugs, the process of micelle formation is more spontaneous for surfactants. The formation of mixed micelles is more spontaneous than the micelle formation of drug.

Adsorption at the air/water interface

Various theories have been developed and applied to study the formation and behavior of monolayers formed in mixed systems [1,12,13]. The interaction parameter, β^{σ}, for the mixed monolayers and the composition of mixed monolayers $\left(X_1^{\sigma}\right)$ are evaluated using the equations

$$\beta^{\sigma} = \frac{\ln\left(\alpha_1 \, conc./X_1^{\sigma} \, conc_1\right)}{\left(1 - X_1^{\sigma}\right)^2} \tag{3.9}$$

and

$$\frac{(X_1^{\sigma})^2 \ln(\alpha_1 conc./X_1^{\sigma} conc_1)}{(1-X_1^{\sigma})^2 [\ln(1-\alpha_1)conc/(1-X_1^{\sigma})conc_2]} = 1 \qquad (3.10)$$

where α_1 is the mole fraction of surfactant in the solution $conc_1$, $conc_2$ and $conc$ are the molar concentrations in the solution of surfactants, drug and their mixture respectively, required to produce a particular γ value (in this calculation γ= 45 mNm^{-1} is fixed).

The β^{σ} values become more negative, which show stronger attractive interaction at the solution/air interface. The β^{σ} values are more negative than β^{m}, which implies that the interaction at the solution/air interface are stronger than in mixed micelles. This is due to the steric factor which is more important in micelle formation than in monolayer formation at a planer interface.

The X_1^{σ} values, calculated by using equation (3.10) and as shown in Tables 3.5 to 3.7, were found to be higher than X_1^{m} values, suggesting that more surfactant is present in mixed monolayer as in the mixed micelles due to the more repulsion between drug and surfactant moieties. The results also indicate that increase in hydrophobic chain length of the surfactants (both gemini and conventional) increases their contribution in mixed monolayer formation, although marginally.

The values of β^{σ} and X_1^{σ} are used to calculate the value of activity coefficients of the two components. f_1^{σ} and f_2^{σ} as

$$f_1^{\sigma} = \exp\{\beta^{\sigma}(1-X_1^{\sigma})^2\} \qquad (3.11)$$

$$f_2^{\sigma} = \exp\left\{\beta^{\sigma}\left(X_1^{\sigma}\right)^2\right\} \tag{3.12}$$

The values of f_1^{σ} and f_2^{σ}, given in Tables 3.5 to 3.7, are always less than unity indicating non-ideality in the system.

The surface excess concentration at the surface saturation, Γ_{max}, is given by equation [25]

$$G_{max} = -\frac{1}{2.303nRT}\left\{\frac{d\gamma}{d\log C}\right\} \tag{3.13}$$

The minimum surface area per molecule (A_{min}) is given by:

$$A_{min} = \frac{1}{N_A \Gamma_{max}} \tag{3.14}$$

where n is introduced to allow simultaneous adsorption of cation and anion. The value of n is used as 2 for pure drug and conventional surfactants, 3 for gemini surfactant and 4 and 5 for drug–conventional and drug–gemini mixtures. Other symbols have their usual meanings. Tables 3.5 to 3.7 bear the values of Γ_{max} and A_{min} for pure components and drug– surfactant mixtures (see Figs. 3.10 to 3.15). As the concentration of surfactants increases in the solution, surface excess also increases. In the absence of surfactants the drug molecules experience more steric as well as electrostatic repulsions and they try to remain far apart from each other. However, as the surfactants are added into the solution they intercalate between the drug molecules and repulsion decreases. As a result, an increase in Γ_{max} takes place. A_{min} follows a trend opposite to that of Γ_{max}.

The molar free energy at the maximum adsorption attained at *cmc*, G_{min}, is calculated using equation (3.15) [26]:

$$G_{min} = \gamma_{cmc} A_{min} N_A \tag{3.15}$$

G_{min} is the minimum free energy of the given surface with fully adsorbed amphiphile molecules. Lower the value of the free energy, more stable is the surface formed. Generally with the increase in mole fraction of surfactant, G_{min} value decreases (Tables 3.5 to 3.7).

The standard Gibb's energy of adsorption, ΔG^{o}_{ads} is related to ΔG^{o}_{m} through the relation [27]

$$\Delta G^{o}_{ads} = \Delta G^{o}_{m} - \frac{\pi_{cmc}}{\Gamma_{max}} \tag{3.16}$$

where π_{cmc} is the surface pressure at the *cmc*, i.e., $\pi_{cmc} = \gamma_o - \gamma_{cmc}$ (γ_o and γ_{cmc} are the surface tensions of pure solvent and mixed system at *cmc*, respectively). The values of ΔG^{o}_{ads} (presented in Tables 3.5 to 3.7) are all negative and the magnitude is greater than ΔG^{o}_{m}. This means that amphiphiles first try to accumulate at the interface and after its saturation these molecules form mixed micelles.

Table 3.1: *Variation of cmc and cmc* for mixed drug– cationic surfactant systems.*

Mole fraction	ADP		NOT		CLP	
	cmc (mM)	*cmc** (mM)	*cmc* (mM)	*cmc** (mM)	*cmc* (mM)	*cmc** (mM)
0	41.0		20.8		18.48	
16-4-16						
0.00025	13.55	30.02	12.78	17.55	10.57	15.87
0.0005	9.66	23.07	10.36	15.17	9.65	13.90
0.001	2.11	16.44	4.20	11.94	2.70	11.14
0.002	1.55	10.44	2.30	8.38	1.56	7.79
1	0.028					
16-5-16						
0.00025	12.97	31.06	12.81	17.90	10.95	16.15
0.0005	10.24	25.00	10.03	15.70	7.78	14.34
0.001	2.41	17.98	3.15	12.61	2.38	11.72
0.002	1.73	11.52	1.73	9.05	1.27	8.58
1	0.032					
16-6-16						
0.00025	13.26	32.30	12.76	18.31	11.10	16.48
0.0005	9.06	26.64	9.52	16.34	9.93	14.87
0.001	2.29	19.73	3.33	13.45	4.47	12.44
0.002	1.36	12.99	2.18	9.94	2.98	9.38
1	0.038					
CTAB						
0.0125	11.67	25.62	8.64	16.02	5.76	14.62
0.02	8.55	20.91	5.15	14.01	4.31	12.99
0.03	6.05	16.79	4.33	12.12	2.15	11.32
0.04	5.28	14.03	3.12	10.64	1.47	10.02
1	0.836					
14-4-14						
0.00025	10.03	38.31	10.39	20.09	10.65	17.92
0.0005	8.15	35.96	8.64	19.42	9.31	17.39
0.001	5.61	32.16	4.56	18.22	2.18	16.41
0.002	3.40	26.26	3.22	16.20	1.82	14.76
1	0.146					

14-5-14						
0.00025	11.21	38.56	11.3	20.16	8.11	17.97
0.0005	8.75	36.39	9.93	19.55	7.81	17.49
0.001	6.21	32.71	5.02	18.44	3.16	16.59
0.002	3.61	27.21	2.22	16.56	1.46	16.58
1						
	0.161					
14-6-14						
0.00025	11.80	38.93	12.63	20.26	9.55	18.05
0.0005	7.55	37.07	8.61	19.74	9.12	14.48
0.001	6.88	33.82	3.75	18.79	2.04	12.44
0.002	3.87	28.78	2.21	17.13	1.43	9.38
1						
	0.192					
TTAB						
0.0125	13.29	36.15	7.28	19.58	5.70	17.51
0.02	11.75	33.77	6.31	18.91	3.59	16.97
0.03	12.17	31.03	5.16	18.09	3.40	16.31
0.04	11.66	28.72	3.45	17.34	1.90	15.69
1	3.40					

Table 3.2: *Various physicochemical parameters (i.e., X_1^m, X_1^{id}, β^m, f_1^m, f_2^m, ΔG_{ex}° and ΔG_m°) for mixed ADP–cationic surfactant systems.*

Mole fraction	X_1^m	X_1^{id}	β^m	f_1^m	f_2^m	ΔG_{ex}° (kJ mol^{-1})	ΔG_m° (kJ mol^{-1})
0							-18.2
16-4-16							
0.00025	0.41	0.27	-3.49	0.29	0.56	-2.1	-20.9
0.0005	0.47	0.42	-3.62	0.37	0.46	-2.3	-21.8
0.001	0.52	0.59	-8.32	0.15	0.11	-5.2	-25.6
0.002	0.55	0.75	-8.09	0.20	0.08	-5.0	-26.4
1							-36.5
16-5-16							
0.00025	0.40	0.24	-3.89	0.25	0.53	-2.4	-21.1
0.0005	0.46	0.39	-3.64	0.35	0.46	-2.3	-21.7
0.001	0.51	0.56	-8.09	0.15	0.12	-5.1	-25.3
0.002	0.55	0.72	-7.94	0.20	0.09	-4.9	-26.1
1							-36.2
16-6-16							
0.00025	0.39	0.21	-4.09	0.22	0.53	-2.5	-21.0
0.0005	0.45	0.35	-4.44	0.26	0.40	-2.8	-21.9
0.001	0.50	0.52	-8.62	0.12	0.11	-5.4	-25.4
0.002	0.53	0.68	-9.27	0.13	0.07	-5.8	-26.8
1							-35.8
CTAB							
0.0125	0.46	0.38	-3.23	0.38	0.51	-2.0	-21.3
0.02	0.50	0.50	-3.58	0.41	0.41	-2.3	-22.1
0.03	0.53	0.60	-4.14	0.41	0.31	-2.6	-23.0
0.04	0.56	0.67	-4.08	0.45	0.28	-2.5	-23.3
1							-21.3
14-4-14							
0.00025	0.36	0.07	-7.43	0.05	0.38	-4.3	-21.7
0.0005	0.39	0.12	-7.21	0.07	0.33	-4.3	-22.2
0.001	0.43	0.22	-7.56	0.08	0.24	-4.7	-23.2
0.002	0.42	0.36	-8.32	0.09	0.16	-5.2	-24.5
1							-32.4

14-5-14							
0.00025	0.35	0.06	-7.95	0.05	0.42	-4.1	-21.4
0.0005	0.39	0.11	-7.07	0.07	0.35	-4.2	-22.1
0.001	0.43	0.20	-7.32	0.09	0.26	-4.5	-22.9
0.002	0.47	0.34	-8.26	0.09	0.16	-5.2	-24.3
1							-32.1
14-6-14							
0.00025	0.34	0.05	-7.14	0.05	0.44	-4.0	-21.3
0.0005	0.39	0.10	-7.97	0.05	0.30	-4.8	-22.4
0.001	0.42	0.18	-7.20	0.08	0.29	-4.0	-22.7
0.002	0.46	0.30	-8.31	0.09	0.17	-5.2	-24.2
1							-31.7
TTAB							
0.00025	0.37	0.13	-5.08	0.13	0.50	-2.9	-21.0
0.0005	0.40	0.19	-4.86	0.17	0.46	-2.9	-21.3
0.001	0.41	0.27	-4.19	0.24	0.48	-2.6	-21.2
0.002	0.43	0.33	-3.89	0.29	0.48	-2.4	-21.3
1							-24.4

Table 3.3: *Various physicochemical parameters (i.e., X_1^m, X_1^{id}, β^m, f_1^m, f_2^m, ΔG_{ex}° and ΔG_m°) for mixed NOT–cationic surfactant systems.*

Mole fraction	X_1^m	X_1^{id}	β^m	f_1^m	f_2^m	ΔG_{ex}° (kJ mol^{-1})	ΔG_m° (kJ mol^{-1})
0							-19.9
16-4-16							
0.00025	0.29	0.16	-1.81	0.40	0.86	-0.9	-21.1
0.0005	0.37	0.27	-1.74	0.50	0.79	-1.0	-21.6
0.001	0.48	0.43	-4.21	0.31	0.38	-2.6	-23.9
0.002	0.53	0.60	-5.24	0.31	0.23	-3.3	-24.6
1							-36.5
16-5-16							
0.00025	0.28	0.14	-1.99	0.36	0.86	-1.0	-21.1
0.0005	0.36	0.25	-2.09	0.43	0.76	-1.2	-21.7
0.001	0.47	0.39	-5.62	0.21	0.29	-3.5	-24.6
0.002	0.52	0.57	-6.65	0.21	0.17	-4.2	-26.1
1							-36.2
16-6-16							
0.00025	0.27	0.12	-2.25	0.31	0.84	-1.1	-21.1
0.0005	0.36	0.21	-2.61	0.35	0.71	-1.5	-21.8
0.001	0.46	0.35	-5.74	0.19	0.29	-3. 6	-24.5
0.002	0.46	0.52	-4.73	0.25	0.37	-2.9	-25.6
1							-35.8
CTAB							
0.0125	0.38	0.24	-2.83	0.34	0.66	-1.7	-22.1
0.02	0.45	0.34	-4.18	0.28	0.44	-2.6	-23.4
0.03	0.48	0.43	-4.15	0.32	0.39	-2.3	-23.8
0.04	0.50	0.51	-4.92	0.30	0.29	-3.1	-24.7
1							-21.3
14-4-14							
0.00025	0.27	0.03	-5.15	0.07	0.68	-2.6	-21.6
0.0005	0.32	0.07	-5.04	0.09	0.61	-2.7	-22.1
0.001	0.39	0.12	-6.78	0.08	0.36	-4.1	-23.7
0.002	0.43	0.22	-7.04	0.10	0.27	-4.4	-24.6
1							-32.4

14-5-14							
0.00025	0.26	0.03	-4.84	0.07	0.73	-2.3	-21.4
0.0005	0.29	0.06	-4.53	0.10	0.67	-2.4	-21.7
0.001	0.38	0.11	-6.53	0.08	0.39	-3.9	-23.5
0.002	0.44	0.21	-8.76	0.06	0.19	-5.4	-25.5
1							-32.1
14-6-14							
0.00025	0.23	0.03	-4.47	0.07	0.79	-2.0	-21.1
0.0005	0.31	0.05	-5.47	0.07	0.60	-2.9	-22.1
0.001	0.39	0.10	-8.05	0.05	0.29	-4.8	-24.2
0.002	0.43	0.18	-9.05	0.05	0.19	-5.6	-25.5
1							-31.7
TTAB							
0.0125	0.34	0.07	-5.78	0.08	0.52	-3.3	-22.5
0.02	0.37	0.11	-5.72	0.10	0.47	-3.3	-22.9
0.03	0.39	0.16	-6.08	0.11	0.39	-3.7	-23.4
0.04	0.42	0.20	-7.29	0.09	0.27	-4.5	-24.4
1							-24.4

Table 3.4: *Various physicochemical parameters (i.e., X_1^m, X_1^{id}, β^m, f_1^m, f_2^m, ΔG_{ex}^o and ΔG_m^o) for mixed CLP–cationic surfactant systems.*

Mole fraction	X_1^m	X_1^{id}	β^m	f_1^m	f_2^m	ΔG_{ex}^o (kJ mol^{-1})	ΔG_m^o (kJ mol^{-1})
0							-20.2
16-4-16							
0.00025	0.30	0.142	-2.33	0.317	0.812	-1.2	-21.6
0.0005	0.35	0.248	-1.73	0.487	0.806	-1.0	-21.8
0.001	0.48	0.398	-5.79	0.203	0.271	-3.6	-25.0
0.002	0.52	0.569	-6.69	0.214	0.164	-4.2	-26.4
1							-36.5
16-5-16							
0.00025	0.29	0.126	-2.35	0.300	0.826	-1.2	-21.5
0.0005	0.37	0.224	-2.87	0.325	0.669	-1.7	-22.4
0.001	0.47	0.366	-6.56	0.158	0.235	-4.1	-25.3
0.002	0.51	0.536	-7.75	0.156	0.133	-4.9	-26.9
1							-36.2
16-6-16							
0.00025	0.28	0.110	-2.59	0.261	0.816	-1.3	-21.5
0.0005	0.33	0.196	-2.06	0.396	0.799	-1.2	-21.7
0.001	0.45	0.327	-4.32	0.264	0.452	-2.7	-23.8
0.002	0.50	0.494	-4.61	0.314	0.317	-2.9	-24.8
1							-36.8
CTAB							
0.0125	0.40	0.219	-4.24	0.216	0.509	-2.6	-23.1
0.02	0.44	0.311	-4.72	0.232	0.394	-2.9	-23.8
0.03	0.48	0.406	-6.73	0.161	0.214	-4.2	-25.6
0.04	0.50	0.479	-7.77	0.141	0.146	-4.9	-26.6
1							-27.3
14-4-14							
0.00025	0.25	0.031	-4.55	0.075	0.762	-2.1	-21.6
0.0005	0.29	0.060	-4.29	0.112	0.705	-2.2	-21.9
0.001	0.41	0.112	-9.59	0.036	0.199	-5.8	-25.6
0.002	0.44	0.202	-9.11	0.057	0.173	-5.7	-26.0
1							-32.4

14-5-14							
0.00025	0.28	0.028	-6.08	0.044	0.612	-3.1	-22.3
0.0005	0.31	0.054	-5.29	0.079	0.608	-2.8	-22.3
0.001	0.40	0.103	-8.20	0.050	0.278	-4.9	-24.6
0.002	0.41	0.187	-10.17	0.041	0.140	-6.3	-26.6
1							-32.1
14-6-14							
0.00025	0.29	0.024	-5.51	0.048	0.690	-2.7	-21.8
0.0005	0.35	0.046	-4.80	0.084	0.680	-2.4	-21.9
0.001	0.47	0.088	-10.49	0.026	0.170	-6.4	-25.7
0.002	0.52	0.162	-10.57	0.034	0.135	-6.5	-26.6
1							-31.7
TTAB							
0.0125	0.35	0.063	-6.58	0.060	0.457	-3.7	-23.1
0.02	0.39	0.098	-7.89	0.053	0.301	-4.7	-24.3
0.03	0.41	0.141	-7.57	0.075	0.280	-4.6	-24.4
0.04	0.44	0.182	-9.57	0.050	0.159	-5.9	-25.9
1							-24.4

Table 3.5: *Interfacial composition (X_1^σ), interaction parameter (β^σ), activity coefficients (f_i^σ) in mixed monolayer and surface properties (Γ_{max}, A_{min}, G_{min} and ΔG°_{ads}) for mixed ADP–cationic surfactant systems.*

Mole fraction	X_1^σ	β^σ	f_1^σ	f_2^σ	$\Gamma_{max}.10^6$ (mol m^{-2})	A_{min} (Å^2)	G_{min} (kJ mol^{-1})	ΔG°_{ads} (kJ mol^{-1})
0					1.734	95.75	24.8	-35.1
16-4-16								
0.00025	0.44	-5.42	0.19	0.35	0.923	179.91	42.3	-56.0
0.0005	0.49	-6.38	0.19	0.22	1.021	162.54	36.3	-54.1
0.001	0.52	-12.35	0.06	0.04	1.110	149.57	31.7	-58.9
0.002	0.54	-12.38	0.07	0.03	1.196	138.80	27.7	-56.6
1					1.616	102.73	26.0	-54.0
16-5-16								
0.00025	0.45	-6.31	0.15	0.28	0.887	187.11	42.9	-57.6
0.0005	0.49	-6.35	0.19	0.21	0.977	169.88	36.9	-56.6
0.001	0.52	-11.41	0.07	0.04	1.075	154.46	32.2	-58.6
0.002	0.55	-11.57	0.09	0.03	1.223	135.71	27.9	-55.7
1					1.405	118.19	29.7	-56.1
16-6-16								
0.00025	0.43	-5.13	0.19	0.38	0.837	198.30	47.8	-56.7
0.0005	0.48	-5.88	0.21	0.25	0.943	176.16	41.5	-54.9
0.001	0.52	-11.03	0.08	0.05	1.107	149.99	33.6	-56.0
0.002	0.54	-12.04	0.08	0.03	1.156	143.68	33.0	-56.2
1					1.236	134.06	33.5	-51.3
CTAB								
0.00025	0.58	-2.68	0.63	0.40	1.044	159.10	36.5	-53.1
0.0005	0.62	-3.32	0.61	0.28	1.154	143.95	32.2	-51.3
0.001	0.63	-4.48	0.54	0.17	1.208	137.41	29.8	-50.9
0.002	0.65	-4.68	0.56	0.14	1.463	113.52	21.3	-49.5
1					2.254	73.65	13.8	-48.9
14-4-14								
0.00025	0.41	-10.21	0.03	0.18	0.756	219.60	47.8	-66.6
0.0005	0.44	-10.77	0.03	0.13	0.809	205.24	41.5	-69.8
0.001	0.46	-9.61	0.06	0.13	0.838	198.22	39.5	-68.5
0.002	0.49	-12.30	0.04	0.05	0.832	199.53	39.7	-70.1
1					1.524	108.93	27.2	-51.1

14-5-14								
0.00025	0.41	-9.49	0.04	0.20	0.820	202.54	45.2	-64.1
0.0005	0.45	-10.97	0.04	0.11	0.853	194.60	40.4	-66.0
0.001	0.47	-9.87	0.06	0.11	0.905	183.56	39.9	-62.8
0.002	0.50	-9.94	0.08	0.08	0.902	183.99	41.0	-64.2
1					1.481	112.15	25.8	-55.7
14-6-14								
0.00025	0.42	-9.78	0.04	0.18	0.762	217.93	47.3	-66.0
0.0005	0.45	-10.91	0.04	0.11	0.807	205.64	42.1	-67.0
0.001	0.47	-8.76	0.09	0.14	0.833	199.21	42.0	-64.8
0.002	0.50	-9.06	0.11	0.10	0.884	187.92	42.8	-60.6
1					1.439	115.31	25.9	-56.2
TTAB								
0.00025	0.42	-4.01	0.26	0.49	1.108	149.80	34.9	-44.7
0.0005	0.46	-4.31	0.29	0.39	1.236	134.32	30.6	-44.3
0.001	0.50	-4.10	0.35	0.36	1.342	123.75	28.5	-43.3
0.002	0.52	-4.30	0.37	0.31	1.405	118.13	16.0	-51.4
1					1.937	85.74	37.4	-44.7

Table 3.6: *Interfacial composition (X_1^σ), interaction parameter (β^σ), activity coefficients (f_i^σ) in mixed monolayer and surface properties (Γ_{max}, A_{min}, G_{min} and ΔG°_{ads}) for mixed NOT–cationic surfactant systems.*

Mole fraction	X_1^σ	β^σ	f_1^σ	f_2^σ	Γ_{max} 10^6 (mol m^{-2})	A_{min} (Å^2)	G_{min} (kJ mol^{-1})	ΔG°_{ads} (kJ mol^{-1})
0					1.652	100.52	26.9	-36.6
16-4-16								
0.00025	0.30	-1.12	0.58	0.90	0.705	235.35	25.6	-59.9
0.0005	0.43	-2.40	0.46	0.64	0.797	208.23	20.6	-60.1
0.001	0.50	-6.54	0.20	0.19	0.807	205.66	17.9	-66.5
0.002	0.54	-6.76	0.25	0.13	0.841	197.44	18.2	-62.9
1					1.616	102.73	26.2	-54.0
16-5-16								
0.00025	0.27	-1.41	0.47	0.90	0.730	227.44	24.7	-55.5
0.0005	0.38	-1.85	0.49	0.77	0.845	196.44	20.9	-52.8
0.001	0.48	-6.03	0.20	0.24	0.846	196.35	20.4	-56.9
0.002	0.52	-9.33	0.12	0.08	0.855	194.19	17.4	-66.0
1					1.405	118.19	30.0	-56.1
16-5-16								
0.00025	0.26	-1.32	0.49	0.91	0.584	284.53	82.2	-61.5
0.0005	0.39	-2.48	0.40	0.68	0.679	244.46	64.1	-64.3
0.001	0.48	-6.44	0.18	0.22	0.795	208.87	51.6	-63.6
0.002	0.52	-6.54	0.22	0.16	0.926	197.23	44.8	-56.4
1					1.236	134.06	33.5	-51.3
CTAB								
0.0125	0.50	-3.08	0.47	0.47	0.752	220.90	51.9	-63.3
0.02	0.55	-3.11	0.53	0.39	0.856	193.90	45.0	-60.6
0.03	0.58	-3.65	0.53	0.29	0.903	183.82	44.3	-57.9
0.04	0.59	-4.58	0.47	0.20	0.912	182.04	42.8	-59.4
1					2.254	73.65	13.8	-48.9
14-4-14								
0.00025	0.36	-7.83	0.04	0.37	0.556	298.38	77.3	-71.0
0.0005	0.38	-7.13	0.07	0.35	0.663	250.47	63.4	-65.3
0.001	0.43	-9.20	0.05	0.18	0.825	201.22	50.3	-61.4
0.002	0.47	-11.02	0.05	0.09	0.884	187.75	46.5	-58.8
1					1.524	108.93	27.2	-51.1

14-5-14								
0.00025	0.36	-7.83	0.04	0.37	0.594	279.65	65.9	-73.5
0.0005	0.38	-7.13	0.07	0.35	0.661	251.31	57.7	-72.3
0.001	0.43	-9.20	0.05	0.18	0.670	247.66	55.9	-72.6
0.002	0.47	-11.02	0.05	0.09	0.716	231.74	51.8	-71.6
1					1.481	112.13	25.8	-55.7
14-6-14								
0.00025	0.29	-4.45	0.11	0.68	0.550	301.63	78.3	-72.4
0.0005	0.38	-6.09	0.09	0.42	0.610	271.97	67.9	-71.7
0.001	0.44	-9.09	0.06	0.17	0.627	264.61	62.3	-76.6
0.002	0.48	-10.53	0.06	0.09	0.884	187.92	42.8	-62.1
1					1.439	115.31	25.9	-56.2
TTAB								
0.0125	0.38	-4.64	0.17	0.50	0.729	227.62	60.3	-59.8
0.02	0.42	-4.74	0.20	0.43	0.849	195.57	51.3	-55.6
0.03	0.46	-5.58	0.19	0.31	0.994	167.09	42.4	-53.5
0.04	0.47	-4.90	0.26	0.33	1.158	143.38	38.9	-46.3
1					1.937	85.74	17.1	-44.7

Table 3.7: *Interfacial composition (X_1^σ), interaction parameter (β^σ), activity coefficients (f_i^σ) in mixed monolayer and surface properties (Γ_{max}, A_{min}, G_{min} and ΔG°_{ads}) for mixed CLP–cationic surfactant systems.*

Mole fraction	X_1^σ	β^σ	f_1^σ	f_2^σ	$\Gamma_{max} \cdot 10^6$ (mol m^{-2})	A_{min} (Å^2)	G_{min} (kJ mol^{-1})	ΔG°_{ads} (kJ mol^{-1})
0					1.610	103.11	29.2	-34.5
16-4-16								
0.00025	0.43	-5.22	0.18	0.39	1.015	163.64	39.5	-52.4
0.0005	0.47	-4.25	0.30	0.39	1.055	157.37	37.9	-50.3
0.001	0.52	-11.31	0.07	0.05	1.238	134.06	31.5	-50.1
0.002	0.54	-11.39	0.09	0.04	1.317	126.07	28.9	-51.8
1					1.616	102.73	25.9	-54.0
16-5-16								
0.00025	0.40	-4.69	0.19	0.47	1.027	161.73	40.9	-50.7
0.0005	0.47	-7.64	0.12	0.19	1.053	157.72	35.2	-55.9
0.001	0.50	-9.56	0.09	0.09	1.119	148.37	34.9	-54.4
0.002	0.53	-12.37	0.03	0.03	1.198	138.55	26.7	-60.8
1					1.405	118.19	29.7	-56.1
16-5-16								
0.00025	0.43	-7.57	0.09	0.25	1.083	153.28	34.2	-51.9
0.0005	0.45	-4.82	0.23	0.38	1.108	149.90	36.1	-49.9
0.001	0.50	-6.74	0.19	0.19	1.161	142.98	33.6	-51.5
0.002	0.53	-10.42	0.10	0.06	1.284	129.31	24.9	-55.8
1					1.236	134.06	33.5	-51.3
CTAB								
0.0125	0.52	-8.82	0.13	0.09	1.203	138.07	30.4	-52.6
0.02	0.54	-9.58	0.13	0.06	1.211	137.15	29.7	-52.8
0.03	0.55	-9.84	0.14	0.05	1.540	107.75	22.7	-48.3
0.04	0.56	-10.97	0.12	0.03	1.560	106.43	22.4	-48.9
1					2.254	73.65	13.8	-48.9
14-4-14								
0.00025	0.37	-8.37	0.04	0.32	1.103	150.49	36.8	-49.2
0.0005	0.40	-7.98	0.06	0.28	1.117	148.62	34.9	-50.5
0.001	0.46	-12.99	0.02	0.06	1.145	145.00	34.1	-53.5
0.002	0.49	-13.02	0.03	0.05	1.734	95.73	21.9	-45.6
1					1.524	108.93	27.2	-51.1

14-5-14								
0.00025	0.37	-7.48	0.05	0.37	0.885	187.51	48.6	-53.3
0.0005	0.40	-7.21	0.08	0.32	0.988	167.98	42.5	-51.3
0.001	0.45	-9.91	0.05	0.13	1.092	152.08	38.0	-51.5
0.002	0.44	-2.48	0.46	0.62	1.151	144.29	35.6	-51.8
1					1.481	112.13	25.8	-55.6
14-6-14								
0.00025	0.37	-7.31	0.06	0.37	0.865	192.02	47.9	-54.8
0.0005	0.41	-7.42	0.08	0.29	1.049	158.24	38.1	-51.5
0.001	0.47	-12.43	0.03	0.06	1.149	144.49	33.9	-54.4
0.002	0.49	-12.59	0.04	0.05	1.134	146.46	33.5	-55.7
1					1.439	155.31	25.9	-56.2
TTAB								
0.0125	0.43	-7.05	0.10	0.27	1.303	127.45	32.6	-45.0
0.02	0.46	-8.37	0.09	0.17	1.399	118.63	29.7	-46.1
0.03	0.49	-9.33	0.09	0.11	1.514	109.68	25.8	-45.6
0.04	0.50	-8.73	0.11	0.11	1.846	89.95	23.3	-41.1
1					1.937	85.74	17.1	-44.7

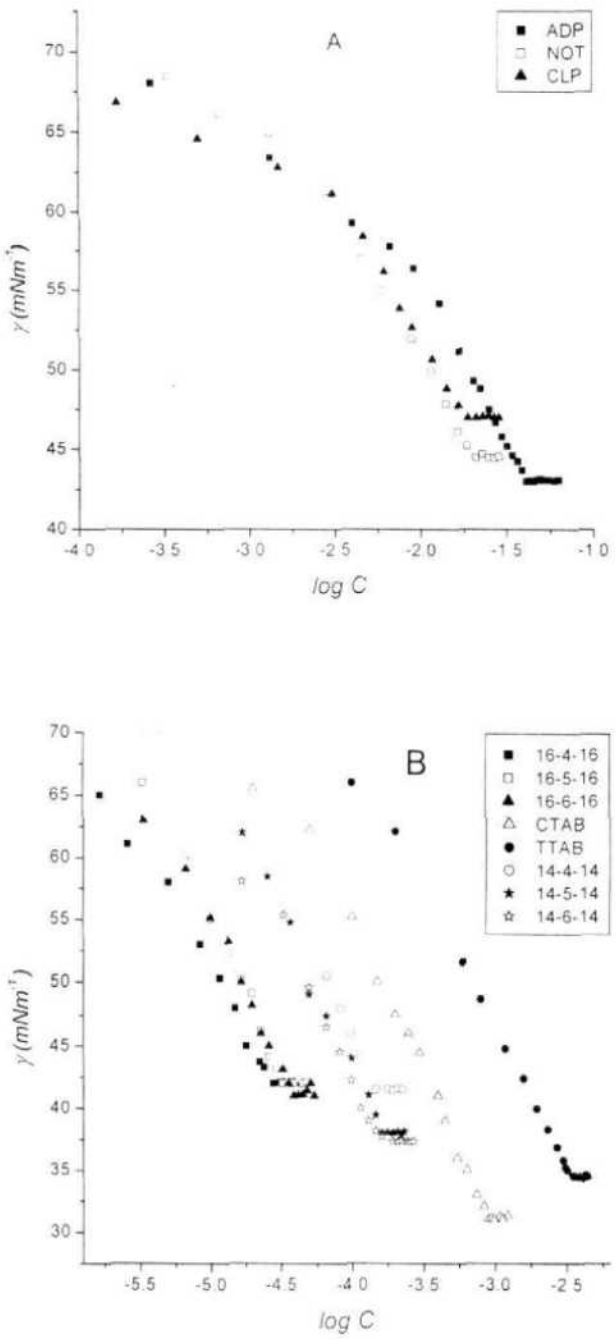


Fig. 3.1: *Plots of surface tension (γ) vs log C of pure drugs (A) (■ ADP, □ NOT and ▲CLP) and pure cationic surfactants (B) (■ 16-4-16, □ 16-5-16, ▲ 16-6-16, Δ CTAB, ● TTAB, o 14-4-14, ★ 14-5-14 and ☆ 14 -6-14).*

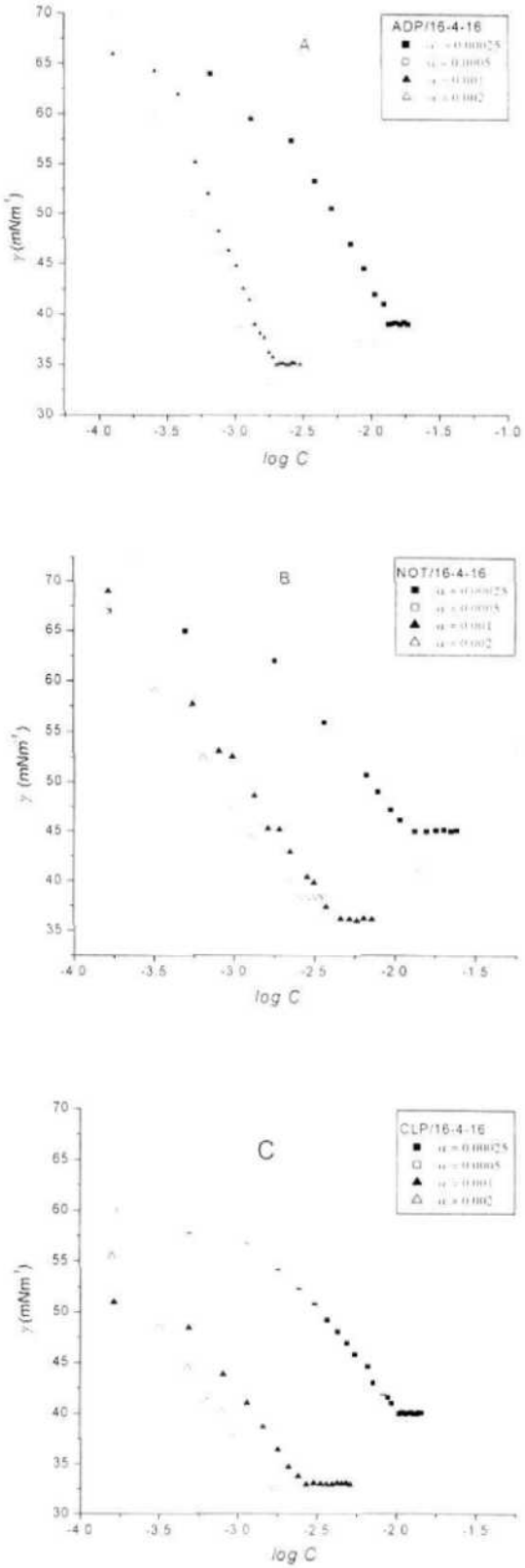


Fig. 3.2: *Plots of surface tension (γ) vs log C of 16-4-16 with ADP (A), NOT (B) and CLP (C) at different mole fractions of 16-4-16 (■ 0.00025, □ 0.0005, ▲ 0.001 and Δ 0.002).*

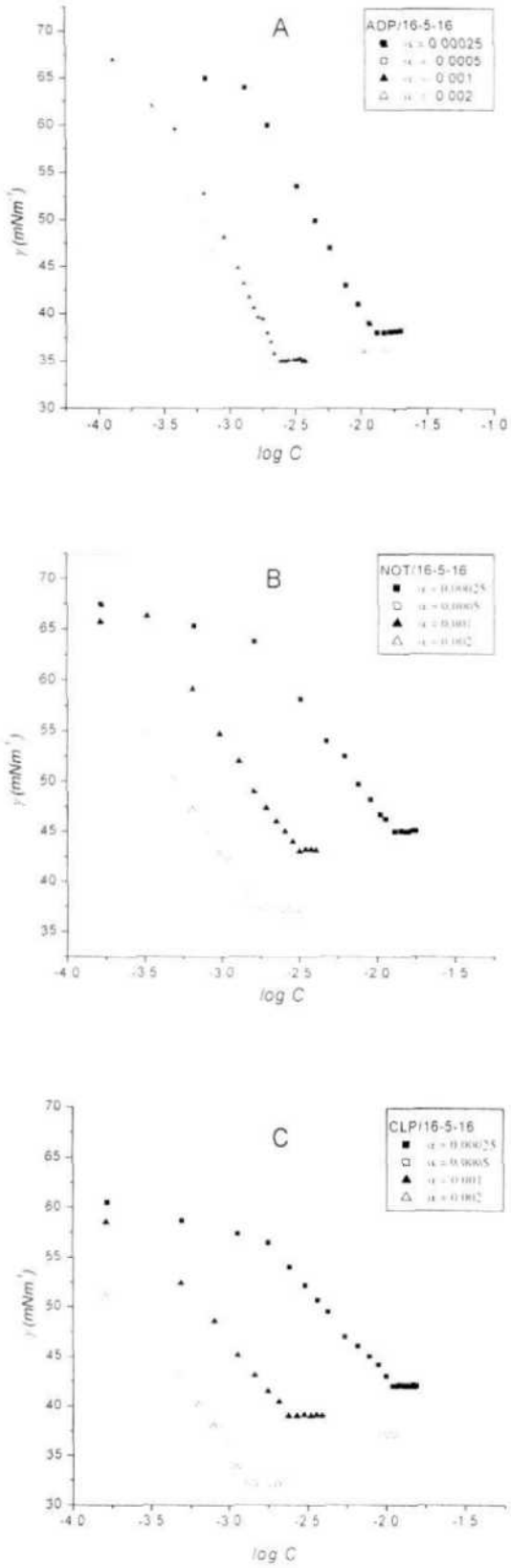


Fig. 3.3: *Plots of surface tension (γ) vs log C of 16-5-16 with ADP (A), NOT (B) and CLP (C) at different mole fractions of 16-5-16 (■ 0.00025, □ 0.0005, ▲ 0.001 and Δ 0.002).*

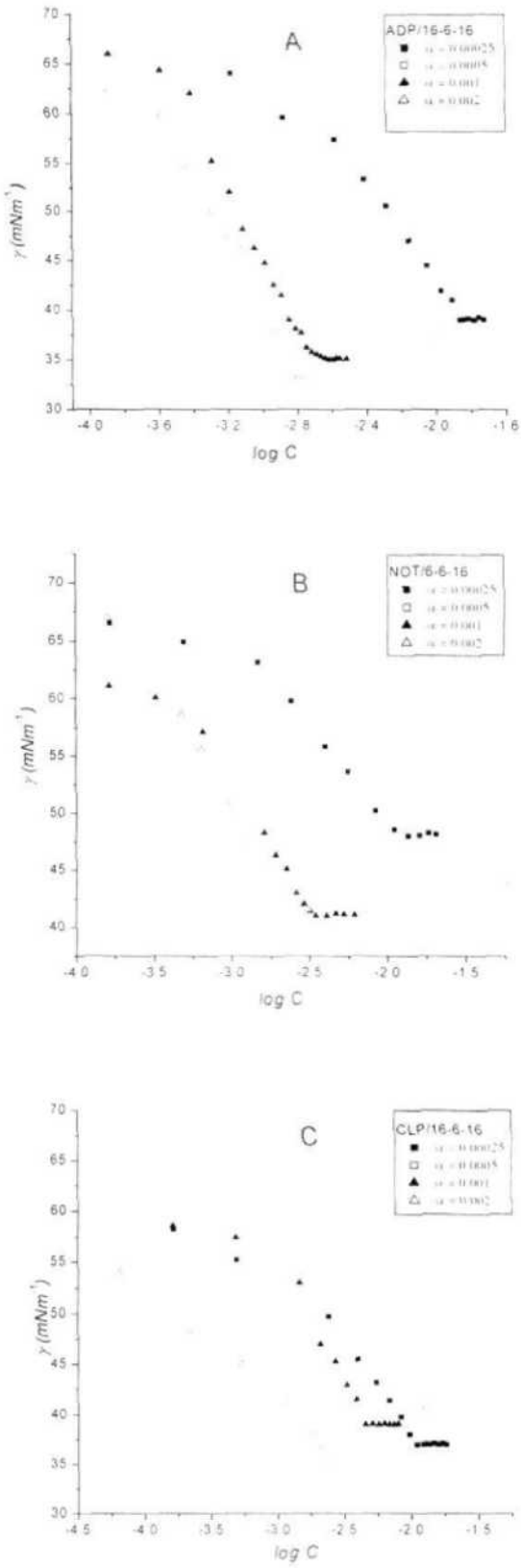


Fig. 3.4: *Plots of surface tension (γ) vs log C of 16-6-16 with ADP (A), NOT (B) and CLP (C) at different mole fractions of 16-6-16 (■ 0.00025, □ 0.0005, ▲ 0.001 and Δ 0.002).*

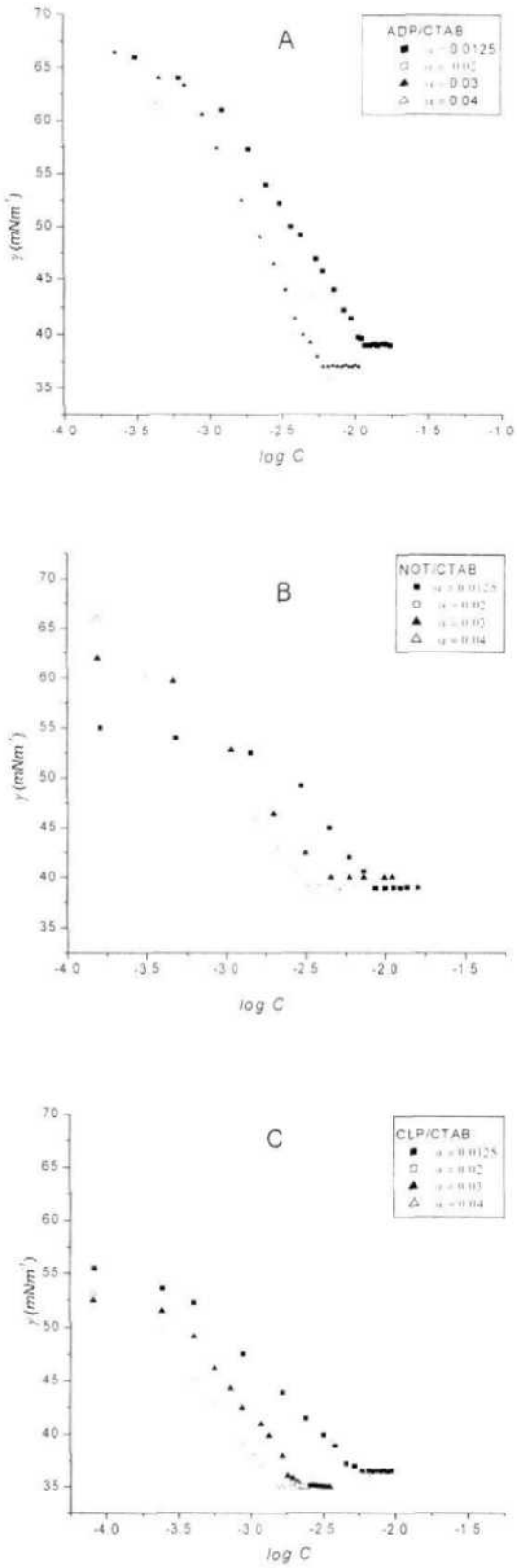


Fig. 3.5: *Plots of surface tension (γ) vs log C of CTAB with ADP (A), NOT (B) and CLP (C) at different mole fractions of CTAB (■ 0.0125, □ 0.02, ▲ 0.03 and Δ 0.04).*

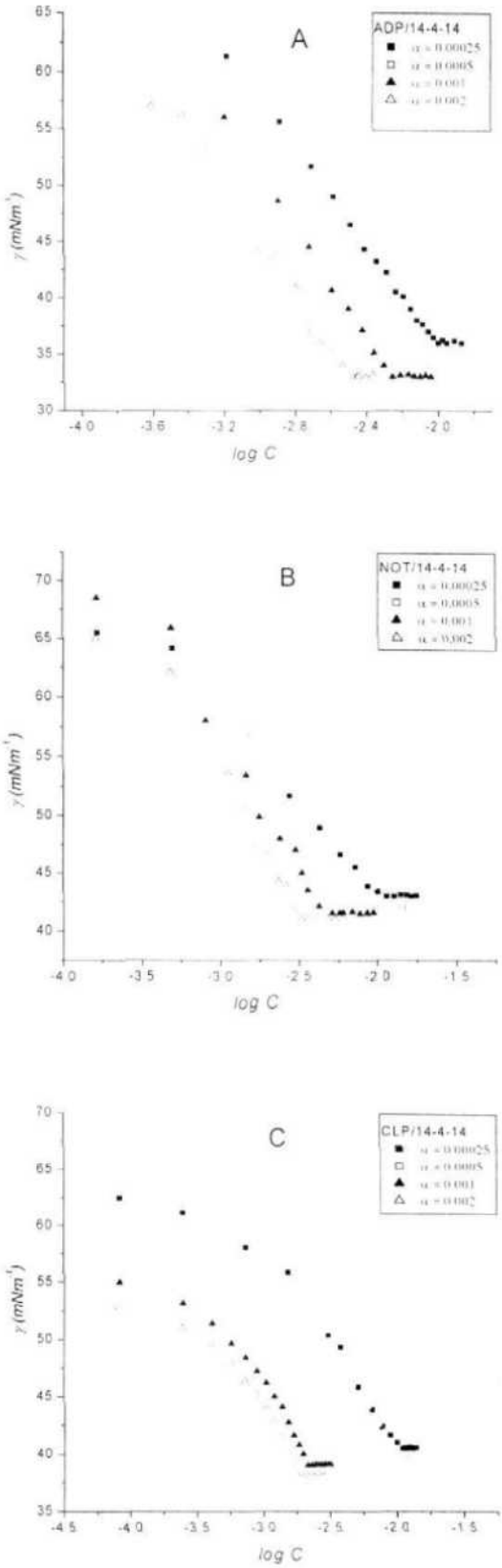


Fig. 3.6: *Plots of surface tension (γ) vs log C of 14-4-14 with ADP (A), NOT (B) and CLP (C) at different mole fractions of 14-4-14 (■ 0.00025, □ 0.0005, ▲ 0.001 and Δ 0.002).*

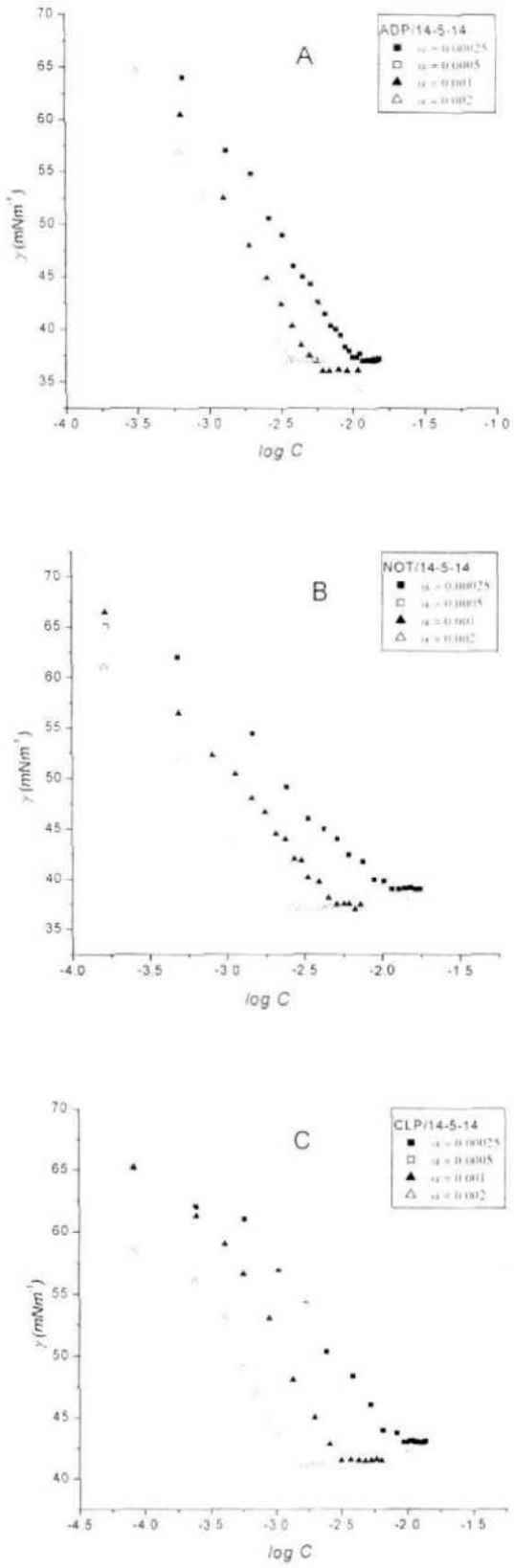


Fig. 3.7: *Plots of surface tension (γ) vs log C of 14-5-14 with ADP (A), NOT (B) and CLP (C) at different mole fractions of 14-5-14 (■ 0.00025, □ 0.0005, ▲ 0.001 and Δ 0.002).*

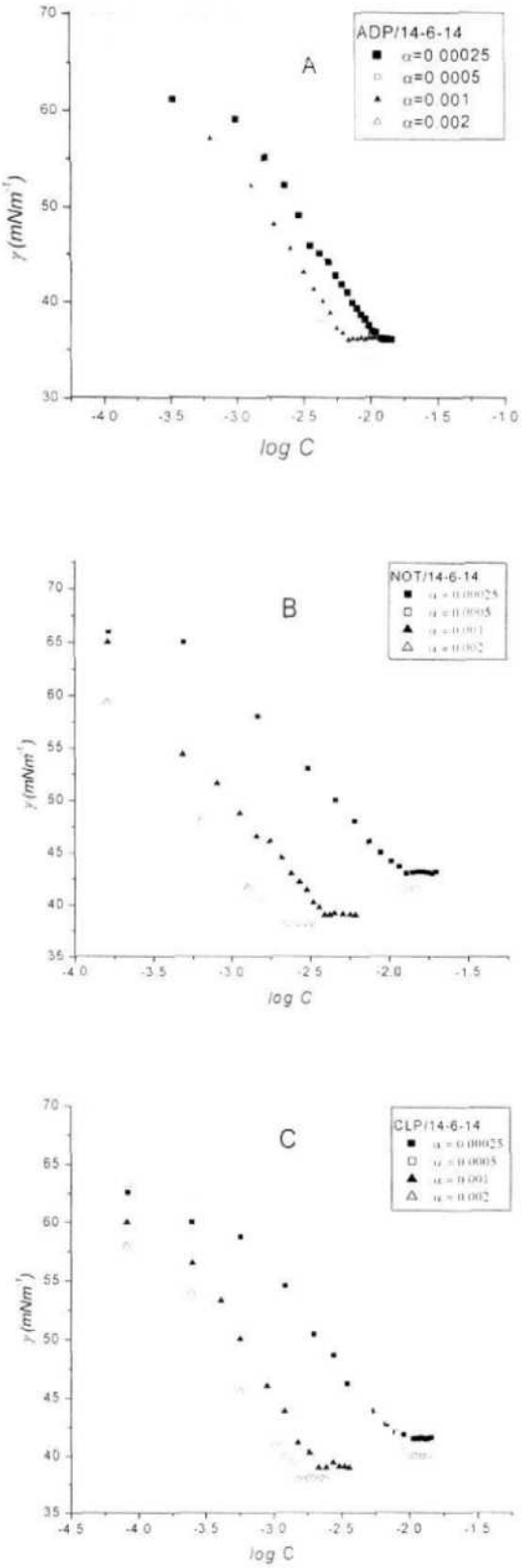


Fig. 3.8: *Plots of surface tension (γ) vs log C of 14-6-14 with ADP (A), NOT (B) and CLP (C) at different mole fractions of 14-6-14 (■ 0.00025, □ 0.0005, ▲ 0.001 and Δ 0.002).*

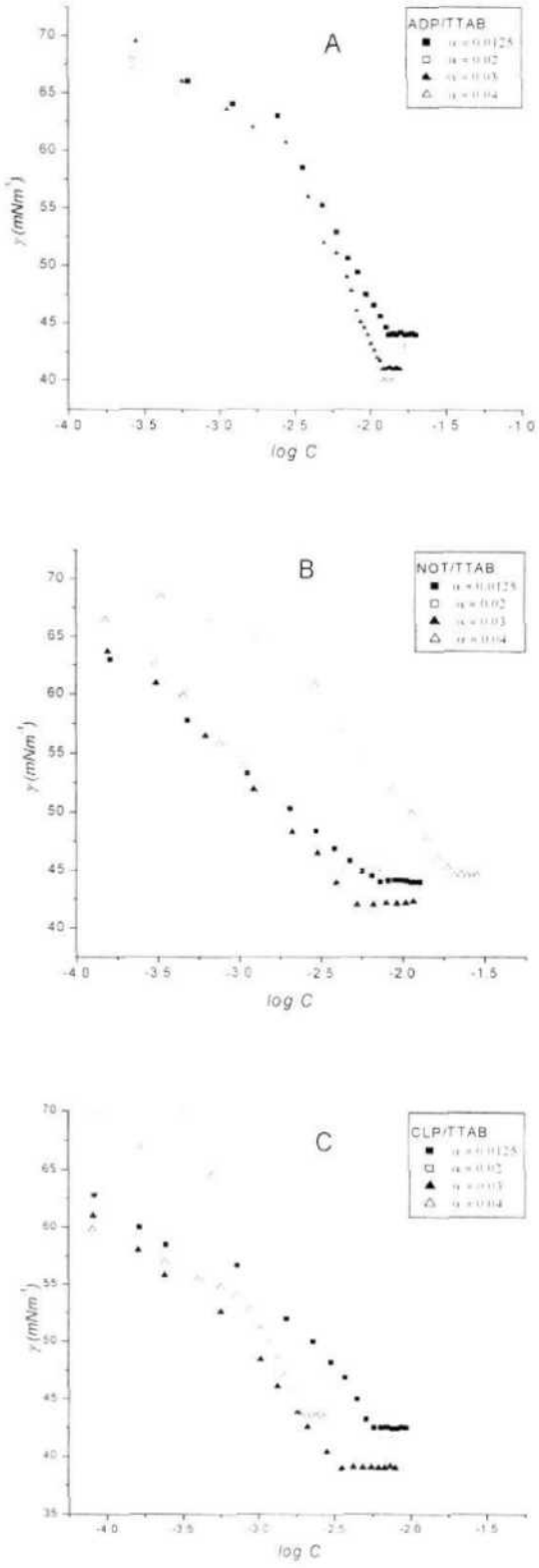


Fig. 3.9: *Plots of surface tension (γ) vs log C of TTAB with ADP (A), NOT (B) and CLP (C) at different mole fractions of TTAB (■ 0.0125, □ 0.02, ▲ 0.03 and Δ 0.04).*

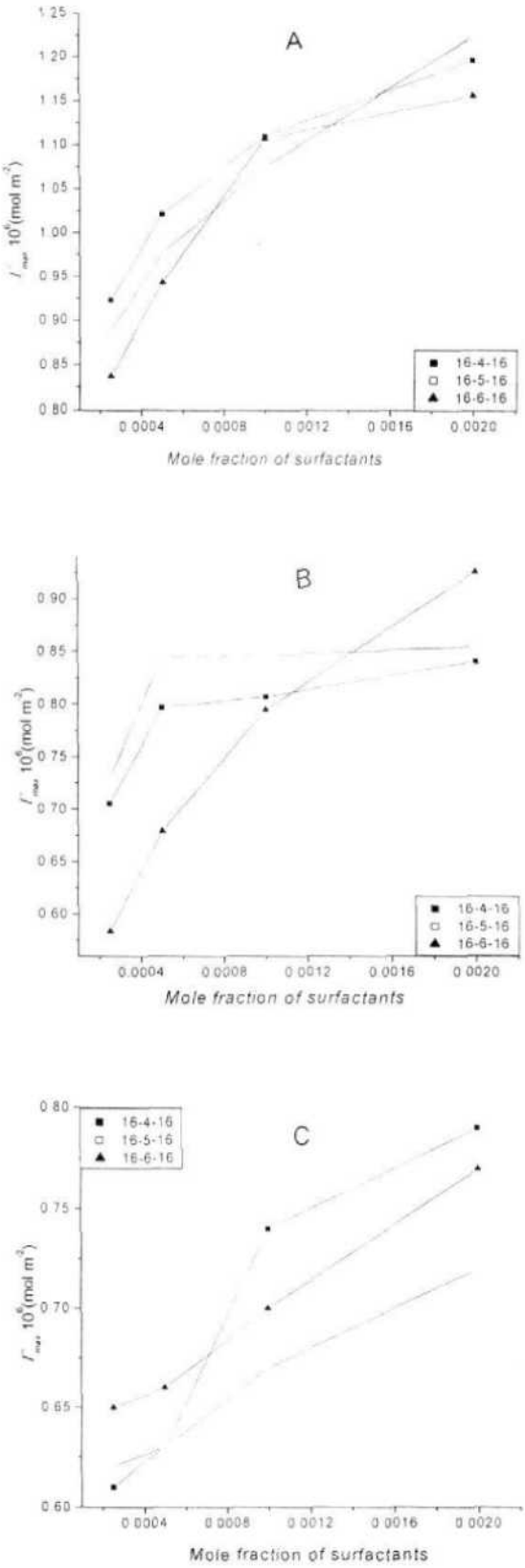


Fig. 3.10: *Variation of Γ_{max} with mole fraction of surfactants for ADP (A), NOT (B) and CLP (C) (■ 16-4-16, □ 16-5-16 and ▲ 16-6-16).*

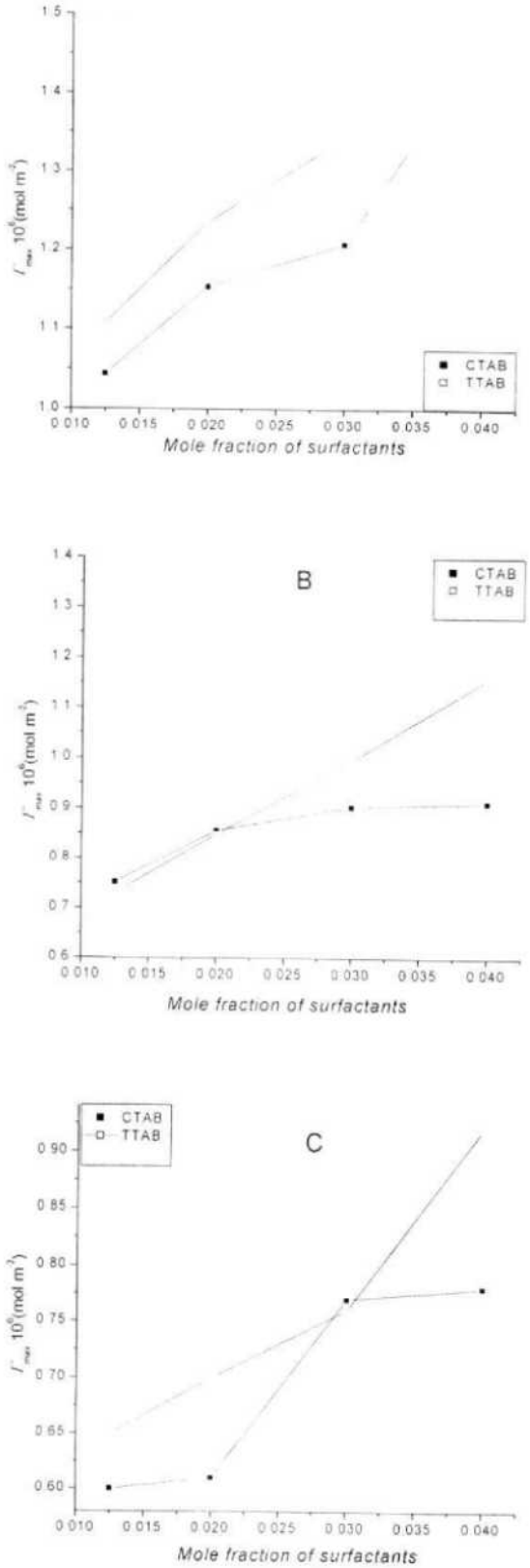


Fig. 3.11: *Variation of Γ_{max} with mole fraction of surfactants for ADP (A), NOT (B) and CLP (C) (■ CTAB and □ TTAB).*

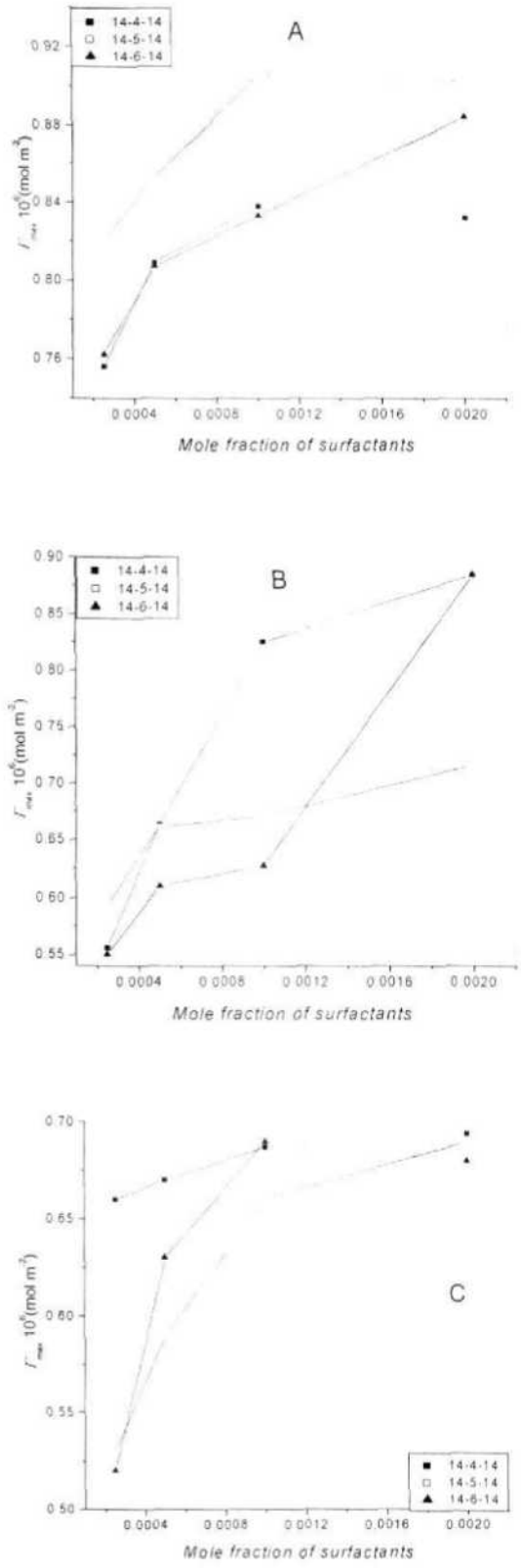


Fig. 3.12: *Variation of Γ_{max} with mole fraction of surfactants for ADP (A), NOT (B) and CLP (C) (■ 14-4-14, □ 14-5-14 and ▲ 14-6-14).*

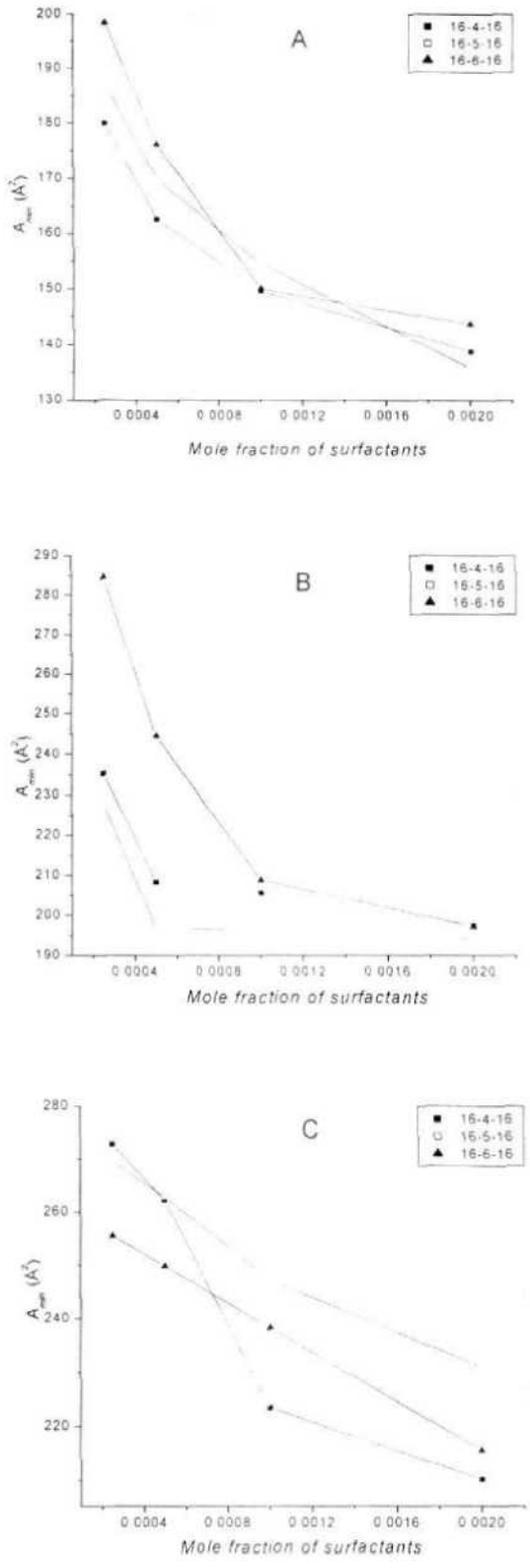


Fig. 3.13: *Variation of A_{min} with mole fraction of surfactants for ADP (A), NOT (B) and CLP (C) (■ 16-4-16, □ 16-5-16 and ▲ 16-6-16).*

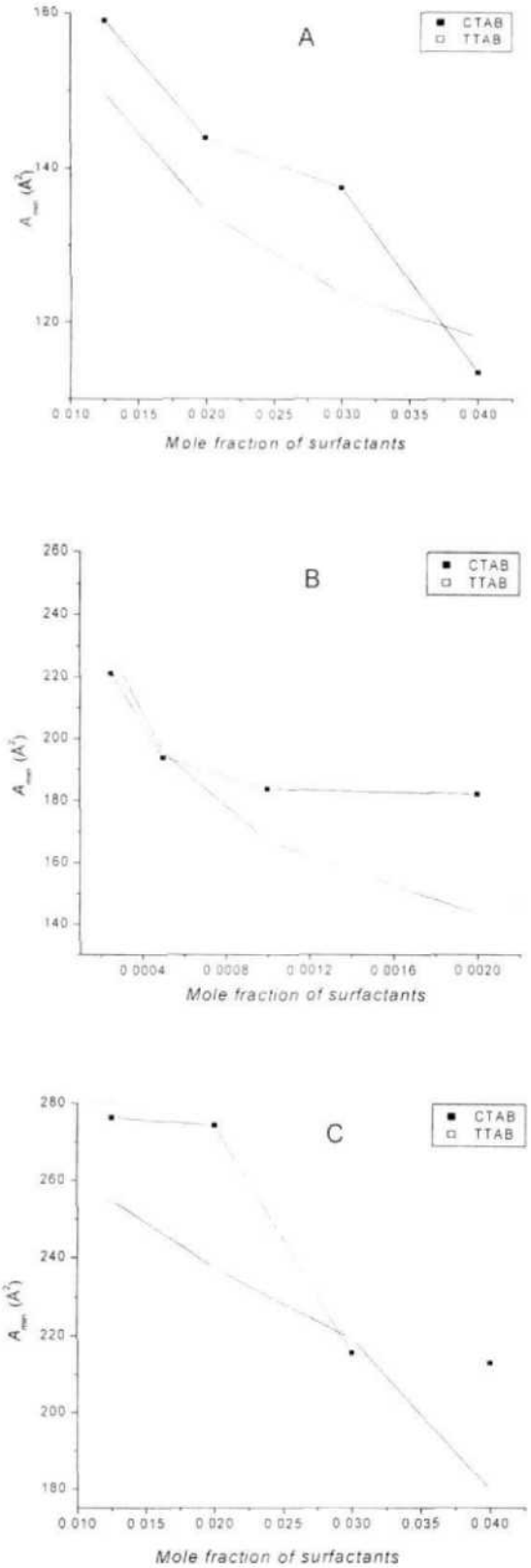


Fig. 3.14: *Variation of A_{min} with mole fraction of surfactants for ADP (A), NOT (B) and CLP (C) (■ CTAB and □ TTAB).*

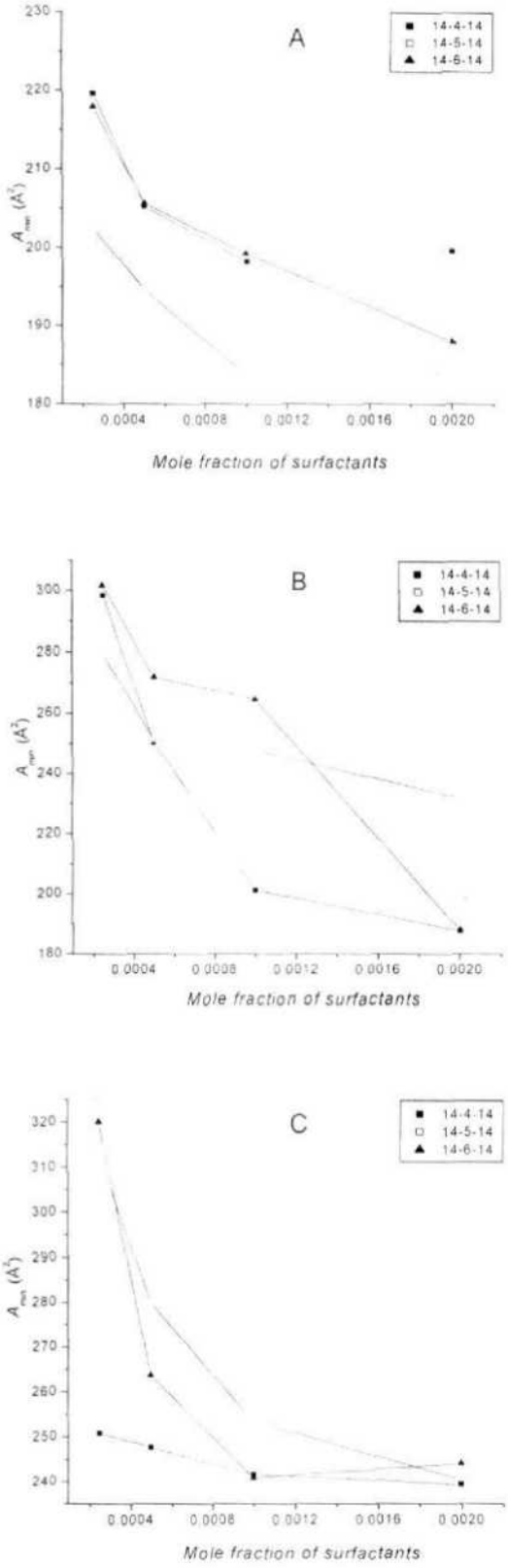


Fig. 3.15: *Variation of A_{min} with mole fraction of surfactants for ADP (A), NOT (B) and CLP (C) (■ 14-4-14, □ 14-5-14 and ▲ 14-6-14).*

(II) Studies with Anionic Surfactants

Anionic surfactants are amphipathic compounds consisting of a hydrophobic and a hydrophilic part. Anionic surfactants not only change the surface characteristics of solids by adsorption but can also enhance the solubility of sparingly soluble compounds in water [28]. Due to their favorable physicochemical characteristics, anionic surfactants are extensively used in many fields of technology and research. Anionic surfactants have been successfully employed for the enhancement of the efficacy of the active ingredient in pharmaceutical [29] and agricultural formulations [30], in biotechnological [31] and in other industrial processes [32].

Bile salts behave like anionic surfactants [33]; however, the formation of bile salt micelles differs from that of the surfactants. These surfactant characteristics result from the combination of the polar hydroxyl groups on the concave α-face and the methyl groups on the convex β-face [34,35]. Bile salts in aqueous solution form aggregates mainly due to hydrophobic attractive interactions of the polar β-faces [36]. However, further stabilization and aggregation occurs through intermolecular hydrogen bonds formation [37,38]. These amphipathic compounds are present in bile as mixed micelles that serve to transport additional cholesterol from the liver into the intestine [39,40] The physiological and therapeutic properties of some bile salts [41] are essentially due to their ability to form both simple and mixed micellar aggregates, which facilitate the dissolution and transportation of lipo-soluble molecules. Mixed micelles of bile salts are promising systems for drug delivery [42]. It has been observed that

the bile salts form mixed micelles with the drugs [43]. Bile salts are known as permeability enhancers to increase drug penetration through various biological membranes by interacting with phospholipids in cell membranes [44,45]. Micelles of bile salts have been investigated in different pharmaceutical formulations where they solubilize poorly soluble drugs [46-49]. The ability of bile salts to achieve this is mainly dependent on their hydrophobicity. Bile salts with more hydrophobic micellar core have greater ability to accept hydrophobic pharmaceutical ingredients [47].

Results and Discussion

Whereas the *cmc's* of pure bile salts, Table 3.8 and Fig. 3.16 are in good agreement with literature [50-52], the experimental *cmc* values of the mixture of the systems (Table 3.8 and Figs. 3.17 to 3.19), show a decrease with increasing concentration of bile salts. The values of *cmc* are deviating from the predicted ideal behavior, which indicates synergism in mixed micelle formation. The deviation of *cmc* values of binary bile salt-drug mixtures from those calculated according to Clint's theory [10], equation (3.1), indicates nonideal behavior of the examined mixtures and the existence of mutual interactions of the components in the micelles.

Both X_1^m and X_1^{id} values increase with increase of bile salt concentrations. As shown in Tables 3.9 to 3.11, the values of X_1^{id} are smaller than X_1^m but are greater than α_1. As the concentration of bile salts increase, their contribution in

mixed micelles also increases. X_1^m values are higher than α_1 indicating that some of the drug molecules are replaced by the bile salts in mixed micelles. X_1^m being greater than X_1^{id} indicates that the micelles rich in bile salts as compared to the mixed micelles at ideal mixing.

The more negative value of β^m interaction parameter indicates stronger synergism between the components. From the results (Tables 3.9 to 3.11), it can be observed that the values of β^m are negative at all molar ratios of the mixture. These values correspond to the deviation between experimentally obtained *cmc* and the calculated *cmc** values and indicate synergism in all investigated bile salt-drug mixtures. The order of hydrophbicity of three bile salts is: NaC < NaTC < NaDC. In spite the NaDC being more hydrophobic than NaC, NaC creates stronger interactions with the investigated drugs. The stronger synergistic effect of NaC compared to NaDC can be explained by the fact that NaC contains tow α-axial hydroxyl groups at C7 and C12 positions, while NaDC has only one α-axial hydroxyl group at C12. Obviously, the number of α-axial hydroxyl groups is important for the stability of the micelles [53].

The values of activity coefficients f_1^m and f_2^m (Tables 3.9 to 3.11), calculated from equations (3.5) and (3.6), are found to be less than unity showing nonideal behavior of the mixed systems.

The negative ΔG_{ex}° values (Tables 3.9 to 3.11) suggest that the mixed micelles are stable than micelles in individual components.

ΔG_m° (the standard Gibbs energy of micellization of the pure and the mixed system) were calculated using equation (3.8). All the values of ΔG_m° are negative indicating that the process of micelle formation is spontaneous. The magnitude of ΔG_m° increase with increase of bile salts concentration in mixed systems, which means the presence of negatively charged bile salts reduces the electrostatic repulsion and makes the process more spontaneous.

The X_1^s values, calculated by using equation (3.10) and given in Tables 3.12 to 3.14, were found to be lower than X_1^m values, suggesting that less surfactant is present in mixed monolayer as in mixed micelles.

The β^σ trend, (Tables 3.12 to 3.14), is similar to β^m i.e., the mixtures of bile salts/drugs show stronger attractive interaction at the solution/air interface. The β^σ values are more negative than the β^m which imply that the interaction at the solution/air interface is stronger than the mixed micelles; this is due to the steric factor which is more important in micelle formation than in monolayer formation at a planar interface. Increased bulkiness in the hydrophobic group causes greater difficulty for incorporation into the curved mixed micelles compared to that of accommodating at the planar interface. The values of activity coefficients, f_1^σ and f_2^σ, (Tables 3.12 to 3.14), are found to be less than unity showing nonideal behavior.

The values of Γ_{max} and A_{min}, calculated by equations (3.13) and (3.14), are given in Tables 3.12 to 3.14 (see also Figs. 3.20 and 3.21). A value of $n = 3$ was

used for mixtures, whereas for pure bile salts $n = 2$ was employed. Γ_{max} increases with increase in the additives (bile salts) concentrations, this indicates that the drug solutions in presence of bile salts have greater preference to be adsorbed at air /water interface, compared to the pure drug solutions. The A_{min} values decrease with increasing additive concentrations (Tables 3.12 to 3.14); this is due to progressive charge shielding and closer packing of drug ions in the surface.

The G_{min} , listed in Tables 3.12 to 3.14, are found to decrease with increasing additive (bile salts) mole fraction. The lower values of G_{min} indicate that the more thermodynamically stable surface is formed.

All ΔG°_{ads} values are negative (Tables 3.12 to 3.14) which imply that the adsorption of amphiphiles at the air /mixture interface takes place spontaneously.

Table 3.8: *Variation of cmc and cmc* for mixed drug-bile salt systems.*

Mole fraction	**ADP**		**NOT**		**CLP**	
	cmc (mM)	*cmc** (mM)	*cmc* (mM)	*cmc** (mM)	*cmc* (mM)	*cmc** (mM)
0	41.0		20.8		18.48	
NaC						
0.0025	10.06	40.63	10.54	20.73	8.60	18.43
0.0037	8.56	40.46	7.79	20.70	8.30	18.41
0.005	7.21	40.28	6.84	20.66	6.75	18.38
0.0062	4.94	40.11	4.96	20.63	5.07	18.36
1	8.92					
NaDC						
0.0025	7.30	38.94	12.81	20.28	11.58	18.07
0.0037	5.36	38.02	9.01	20.04	7.65	17.89
0.005	4.35	37.08	8.04	19.79	6.61	17.69
0.0062	3.41	36.25	6.59	19.56	3.88	17.50
1	1.85					
NaTC						
0.0025	17.83	40.34	12.59	20.65	10.47	18.37
0.0037	16.12	40.02	9.46	20.58	7.91	18.32
0.005	14.06	38.70	5.60	20.51	6.83	18.26
0.0062	10.63	39.40	3.19	20.44	4.61	18.21
1	5.42					

Table 3.9: *Various physicochemical parameters (i.e., X_1^m, X_1^{id}, β^m, f_1^m, f_2^m, ΔG_{ex}° and ΔG_m°) for mixed ADP–bile salt systems.*

Mole fraction	X_1^m	X_1^{id}	β^m	f_1^m	f_2^m	ΔG_{ex}° (kJ mol^{-1})	ΔG_m° (kJ mol^{-1})
0							-18.2
NaC							
0.0025	0.32	0.01	-10.15	0.009	0.359	-5.5	-21.7
0.0037	0.34	0.02	-10.30	0.011	0.313	-5.8	-22.1
0.005	0.35	0.02	-10.61	0.012	0.270	-6.1	-22.5
0.0062	0.37	0.03	-11.92	0.009	0.191	-7.0	-23.5
1							-22.0
NaDC							
0.0025	0.37	0.05	-9.20	0.027	0.280	-5.4	-22.5
0.0037	0.39	0.08	-9.85	0.027	0.215	-5.9	-23.3
0.005	0.41	0.10	-10.22	0.029	0.179	-6.2	-23.6
0.0062	0.42	0.12	-10.86	0.027	0.143	-6.9	-24.4
1							-25.7
NaTC							
0.0025	0.28	0.02	-6.71	0.30	0.599	-3.4	-20.3
0.0037	0.30	0.03	-6.66	0.037	0.559	-3.5	-20.5
0.005	0.31	0.04	-6.87	0.041	0.500	-3.8	-20.9
0.0062	0.35	0.04	-7.81	0.035	0.394	-4.5	-21.6
1							-23.3

Table 3.10: *Various physicochemical parameters (i.e., X_1^m, X_1^{id}, β^m, f_1^m, f_2^m, ΔG_{ex}° and ΔG_m°) for mixed NOT–bile salt systems.*

Mole fraction	X_1^m	X_1^{id}	β^m	f_1^m	f_2^m	ΔG_{ex}° (kJ mol^{-1})	ΔG_m° (kJ mol^{-1})
0							-19.9
NaC							
0.0025	0.24	0.006	-7.50	0.013	0.66	-3.4	-21.6
0.0037	0.28	0.009	-8.60	0.012	0.51	-4.4	-22.4
0.005	0.30	0.012	-8.89	0.013	0.45	-4.7	-22.7
0.0062	0.33	0.014	-10.16	0.010	0.33	-5.7	-23.5
1							-22.0
NaDC							
0.0025	0.23	0.027	-4.36	0.075	0.79	-1.9	-51.1
0.0037	0.30	0.040	-5.74	0.060	0.59	-3.0	-51.3
0.005	0.32	0.053	-5.82	0.068	0.55	-3.2	-46.3
0.0062	0.35	0.066	-6.41	0.064	0.47	-3.7	-51.4
1							-25.7
NaTC							
0.0025	0.22	0.010	-5.97	0.026	0.75	-2.6	-21.1
0.0037	0.28	0.014	-7.14	0.023	0.58	-3.6	-21.9
0.005	0.33	0.019	-9.26	0.016	0.37	-5.2	-23.2
0.0062	0.38	0.023	-11.63	0.010	0.20	-6.8	-24.6
1							-23.3

Table 3.11: *Various physicochemical parameters (i.e., X_1^m, X_1^{id}, β^m, f_1^m, f_2^m, ΔG_{ex}° and ΔG_m°) for mixed CLP–bile salt systems.*

Mole fraction	X_1^m	X_1^{id}	β^m	f_1^m	f_2^m	ΔG_{ex}° (kJ mol^{-1})	ΔG_m° (kJ mol^{-1})
0							-20.2
NaC							
0.0025	0.25	0.006	-8.10	0.010	0.164	-3.78	-20.7
0.0037	0.27	0.008	-7.78	0.013	0.600	-3.73	-21.2
0.005	0.29	0.010	-8.45	0.013	0.503	-4.34	-21.9
0.0062	0.32	0.013	-9.75	0.011	0.369	-5.34	-22.4
1							-22.0
NaDC							
0.0025	0.22	0.024	-4.40	0.070	0.803	-1.92	-23.3
0.0037	0.30	0.036	-6.07	0.051	0.579	-3.21	-24.6
0.005	0.32	0.048	-6.29	0.055	0.521	-3.46	-25.1
0.0062	0.30	0.059	-6.41	0.043	0.562	-3.39	-25.7
1							
NaTC							
0.0025	0.23	0.009	-6.52	0.021	0.71	-2.91	-23.0
0.0037	0.28	0.012	-7.62	0.019	0.55	-3.87	-23.9
0.005	0.30	0.017	-7.97	0.021	0.48	-4.24	-24.1
0.0062	0.34	0.028	-9.50	0.016	0.33	-5.40	-26.0
1							-23.3

Table 3.12: *Interfacial composition (X_1^σ), interaction parameter (β^σ), activity coefficients (f_i^σ) in mixed monolayer and surface properties (Γ_{max}, A_{min}, G_{min} and ΔG°_{ads}) for mixed ADP–bile salt systems.*

Mole fraction	X_1^σ	β^σ	f_1^σ	f_2^σ	$\Gamma_{max}.10^6$ (mol m^{-2})	A_{min} (Å^2)	G_{min} (kJ mol^{-1})	ΔG°_{ads} (kJ mol^{-1})
0					1.734	95.76	24.8	-34.6
NaC								
0.0025					0.389	426.92	129.7	-77.1
0.0037					0.411	404.44	131.5	-63.5
0.005					0.467	355.26	112.5	-62.9
0.0062					0.579	286.67	90.0	-57.8
1					0.973	170.68	50.3	-45.1
NaDC								
0.0025					0.391	424.59	127.9	-76.2
0.0037	0.30	-6.28	0.09	0.56	0.440	377.33	111.4	-71.0
0.005	0.29	-4.85	0.01	0.68	0.443	374.52	111.1	-74.9
0.0062	0.38	-10.02	0.72	0.23	0.478	347.21	97.2	-78.8
1					0.903	183.95	53.5	-51.9
NaTC								
0.0025					0.648	256.39	75.7	-55.5
0.0037	0.24	-6.81	0.01	0.68	0.728	228.04	63.4	-55.9
0.005	0.30	-9.01	0.01	0.44	0.731	227.27	58.9	-60.8
0.0062	0.31	-8.92	0.49	0.42	0.828	204.42	54.3	-54.2
1					0.799	207.55	61.2	-52.0

Table 3.13: *Interfacial composition (X_1^σ), interaction parameter (β^σ), activity coefficient (f_i^σ) in mixed monolayer and surface properties (Γ_{max}, A_{min}, G_{min} and ΔG°_{ads}) for mixed NOT–bile salt systems.*

Mole fracton	X_1^σ	β^σ	f_1^σ	f_2^σ	$\Gamma_{max}.10^6$ (mol m^{-2})	A_{min} (Å^2)	G_{min} (kJ mol^{-1})	ΔG°_{ads} (kJ mol^{-1})
0					1.652	100.52	26.9	-36.5
NaC								
0.0025					0.857	193.85	48.6	-57.0
0.0037					0.877	189.28	55.9	-47.4
0.005	0.21	-6.81	0.014	0.74	0.957	173.42	51.2	-46.1
0.0062	0.24	-6.87	0.413	0.71	0.979	169.56	47.1	-50.4
1					0.973	170.68	50.4	-45.1
NaDC								
0.0025	0.26	-6.74	0.002	0.64	0.933	177.93	46.1	-51.1
0.0037	0.39	-15.79	0.166	0.09	0.941	176.42	46.8	-51.3
0.005	0.25	-4.86	0.032	0.75	0.998	166.06	47.0	-46.3
0.0062	0.38	-11.72	0.880	0.18	1.134	146.40	34.8	-51.4
1					0.903	183.95	53.8	-51.9
NaTC								
0.0025					0.713	232.99	70.2	-52.0
0.0037					0.736	225.60	67.9	-52.4
0.005	0.19	-5.57		0.82	0.742	223.67	66.0	-53.8
0.0062					0.762	217.82	64.3	-54.5
1					0.799	207.55	61.5	-52.0

Table 3.14: *Interfacial composition (X_1^σ), interaction parameter (β^σ), activity coefficients (f_i^σ) in mixed monolayer and surface properties (Γ_{max}, A_{min}, G_{min} and ΔG°_{ads}) for mixed CLP–bile salt systems.*

Mole fraction	X_1^σ	β^σ	f_1^σ	f_2^σ	$\Gamma_{max}.10^6$ (mol m^{-2})	A_{min} (Å^2)	G_{min} (kJmol^{-1})	ΔG°_{ads} (kJmol^{-1})
0					1.610	103.11	24.8	-34.5
NaC								
0.0025	0.34	-15.63	0.47	0.16	0.665	294.87	61.7	-65.7
0.0037	0.35	-15.31	0.47	0.15	0.714	232.55	56.7	-64.9
0.005	0.36	-14.97	0.40	0.15	0.779	213.31	53.3	-61.2
0.0062	0.37	-16.35	0.29	0.11	0.809	205.26	51.3	-60.7
1					0.973	170.68	50.7	-45.1
NaDC								
0.0025	0.33	-9.38	0.58	0.37	0.674	246.53	63.8	-64.4
0.0037	0.35	-10.02	0.45	0.29	0.824	201.51	51.6	-58.8
0.005	0.34	-12.40	0.31	0.14	0.833	199.43	49.8	-60.1
0.0062	0.42	-17.65	0.51	0.04	0.862	192.65	42.9	-65.8
1					0.903	183.95	53.5	-51.9
NaTC								
0.0025	0.27	-9.57	0.56	0.50	0.661	251.17	67.3	-61.6
0.0037	0.32	-11.61	0.55	0.30	0.672	246.98	65.4	-63.1
0.005	0.34	-12.36	0.42	0.24	0.711	233.51	61.2	-62.3
0.0062	0.37	-15.03	0.54	0.13	0.715	232.11	60.1	-64.0
1					0.799	207.55	61.5	-52.0

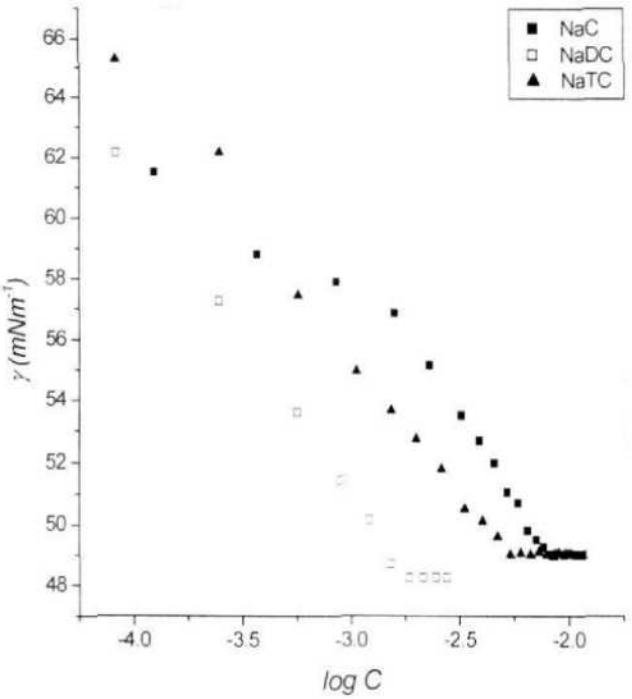


Fig. 3.16: *Plots of surface tension (γ) vs log C of pure bile salt* (■ *NaC*, □ *NaDC*, ▲ *NaTC*).

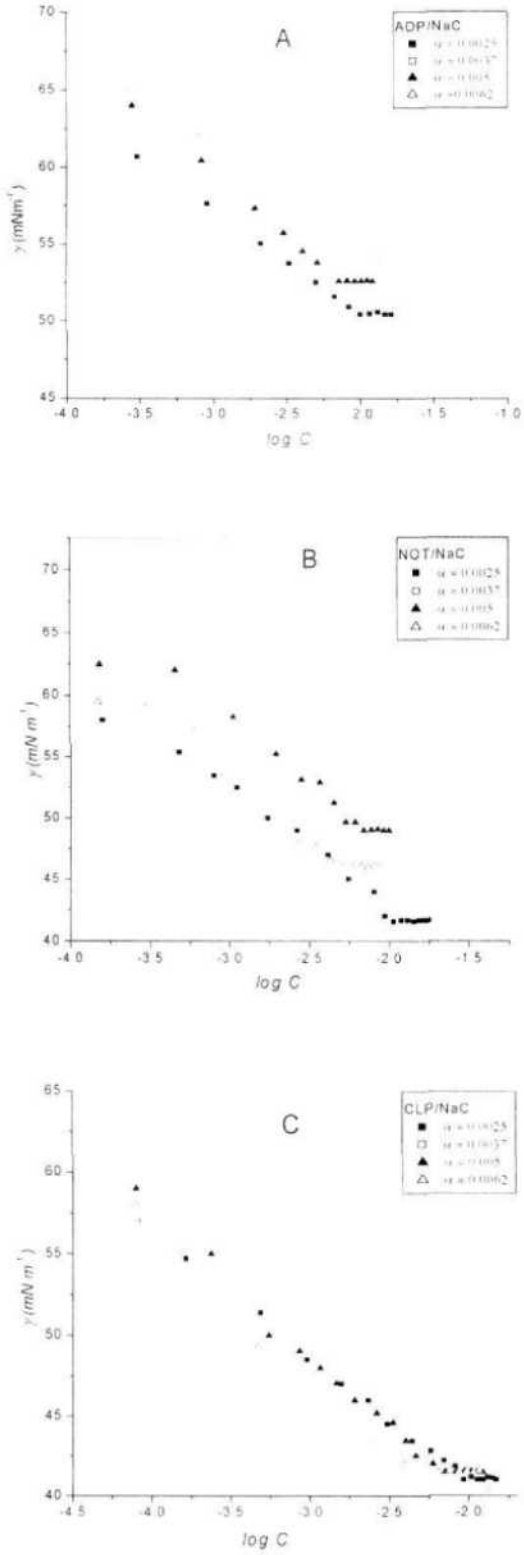


Fig. 3.17: *Plots of surface tension (γ) vs log C of NaC with ADP (A), NOT (B) and CLP (C) at different mole fractions of NaC (■ 0.0025, □ 0.0037, ▲ 0.005 and Δ 0.0062).*

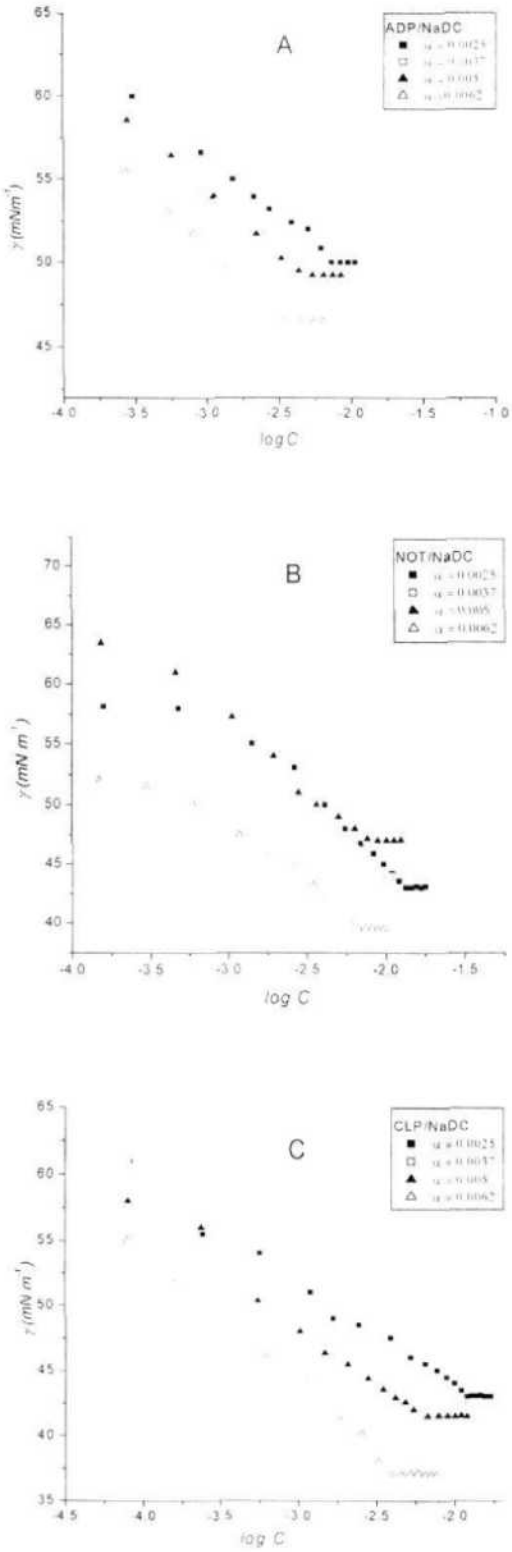


Fig. 3.18: *Plots of surface tension (γ) vs log C of NaDC with ADP (A), NOT (B) and CLP (C) at different mole fractions of NaDC (■ 0.0025, □ 0.0037, ▲ 0.00and Δ 0.0062).*

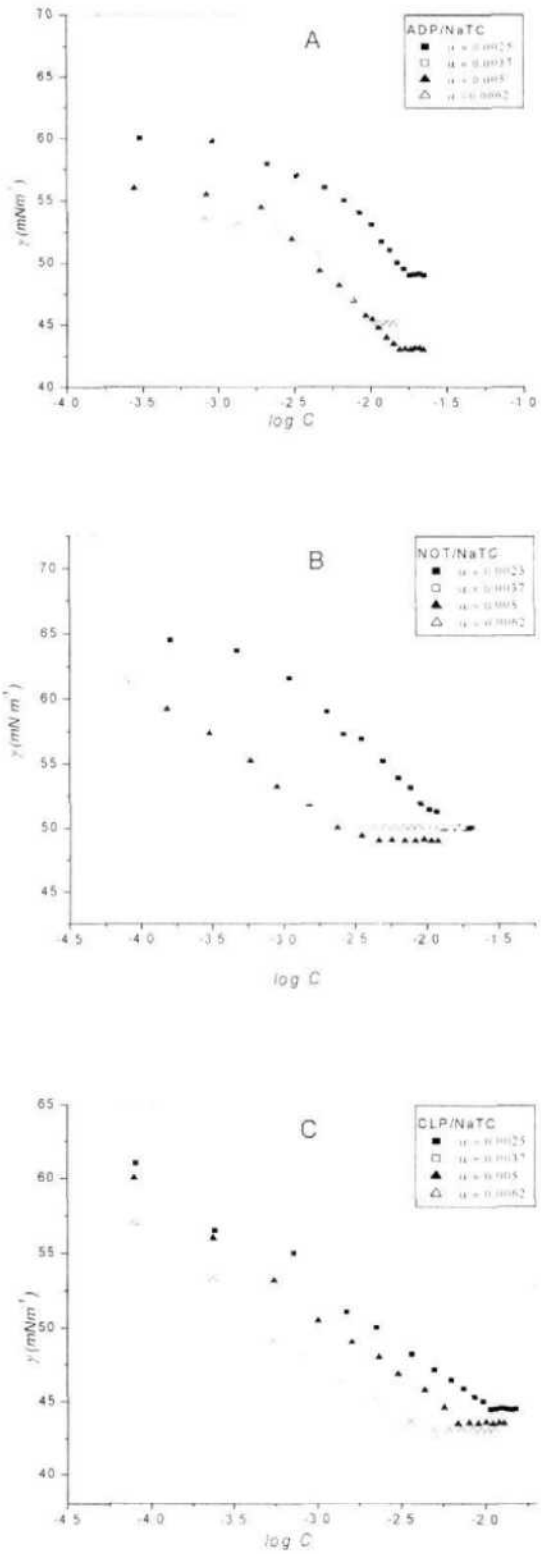


Fig. 3.19: *Plots of surface tension (γ) vs log C of NaTC with ADP (A), NOT (B) and CLP (C) at different mole fractions of NaTC (■ 0.0025, □ 0.0037, ▲ 0.005 and Δ 0.0062).*

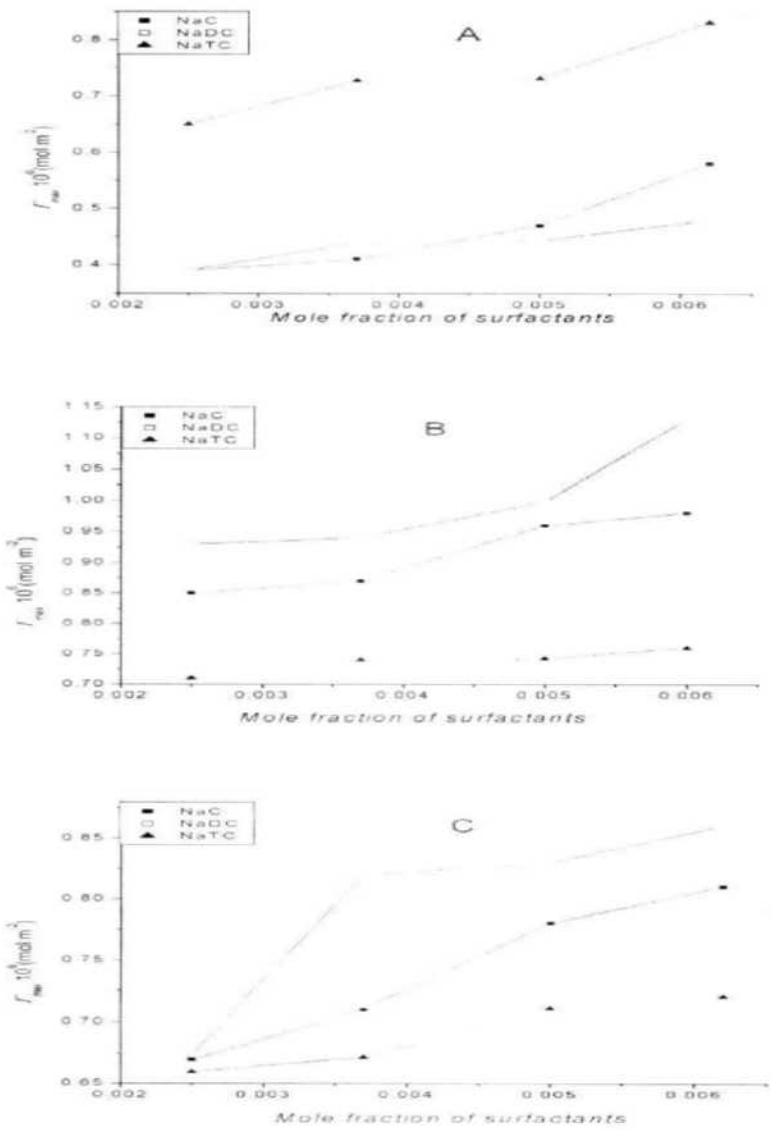


Fig. 3.20: *Variation of Γ_{max} with mole fraction of surfactants for ADP (A), NOT (B) and CLP (C)* (■ *NaC*, □ *NaDC* and ▲ *NaTC*).

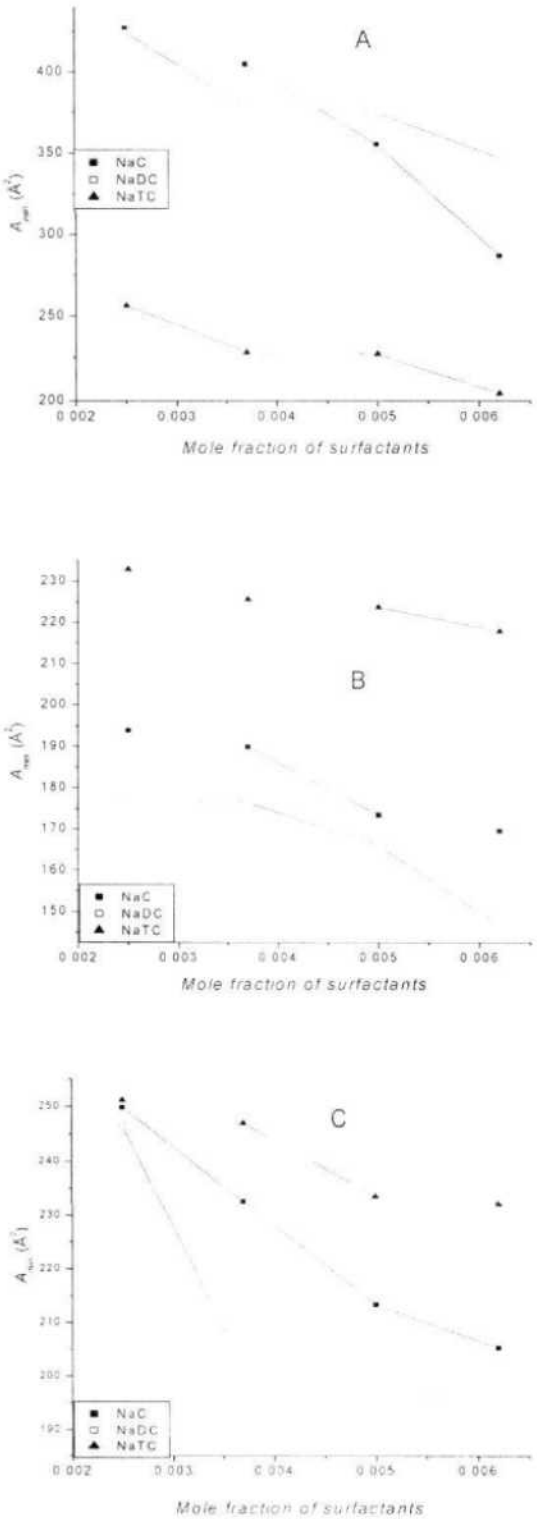


Fig. 3.21: *Variation of A_{min} with mole fraction of surfactants for ADP (A), NOT (B) and CLP (C)* (■ *NaC*, □ *NaDC* and ▲ *NaTC*).

(III) Studies with Nonionic Surfactants

Nonionic surfactants, due to their favorable physicochemical properties, are used in pharmaceuticals to increase their stability [54] and to enhance the dissolution rate of active ingredients from suppositories [55] and solid dispersions [56]. These surfactants are also used to facilitate solubilization [57] and to increase the stability of drug carrier emulsions [58]. Some of the surfactants used in pharmaceutical formulations are Cremophor EL [59], Tween 80 [60], Triton X-100 [61], Poloxamers [62], Brij 54 [63], Cremophor RX-40 [64], Cetrimide [63], etc.

Triblock copolymers of the type poly (ethylene oxide) – poly (propylene oxide)- poly(ethylene oxide) (PEO-PPO-PEO) are members from nonionic surfactants. They have found widespread industrial and commercial applications as emulsifying, wetting, thickening, coating, solubilizing, stabilizing dispersing, lubricating and foaming agents [65]. Amphiphilic block copolymers have proven to be one of the most promising families for use in micellar drug formulation and delivery. They are highly versatile materials as they may be synthesized to suit specific applications. In aqueous media, the amphiphilic copolymers self-assemble to form nano-sized micelles that include a hydrophobic core surrounded by hydrophilic corona. The hydrophobic core of micelles may be used for solubilization of hydrophobic drugs. In few cases block copolymer micelles have been proven to function as true carriers meaning that have been shown to be capable of retaining the drug until reaching the target/desired site [66].

Results and Discussion

The *cmc* values for pure surfactants agree well with the literature values [67] and the values of *cmc* of the mixed systems, given in Table 3.15 (see also Figs. 3.22 to 3.26), show that the *cmc* values decrease with the increase in stoichiometric mole fraction of nonionic surfactants (α_1). The values fall in between those of the pure components. This means that the two components form mixed micelles. At α_1 = 0.0015 of Tween 40, the *cmc* value for the ADP-surfactant system shows a sharp decrease from 41.0 to 8.86 mM. For α_1 higher than 0.0015, although *cmc* values decrease, the rate is slower, i.e., from 8.86 to 2.8 mM when α_1 changes from 0.0015 to 0.006. Similar is the trend with other surfactants as well as with NOT-surfactant and CLP-surfactant systems. The presence of nonionic surfactants in between the positively charged heads of drug monomers reduces the inter head group repulsions and makes micellization easier.

We get that the ideal *cmc* values *cmc** are always greater than the experimentally determined *cmc* values. The negative deviation from ideality indicates attractive interactions between the two components forming the mixed micelles. Reduction in repulsions among head groups, ion-dipole interactions among cationic–nonionic head groups, and hydrophobic interactions lead to negative deviation of the system from ideality.

Micelle mole fraction (X_1^m) values, calculated according to equation (3.2), are given in Tables 3.16 to 3.18. These values (except for α_1 = 0.006 for Tween 40, Tween 80, P85 with ADP and Tween 40 with NOT) increase continuously

with α_1. Except in NOT- P85 systems, X_1^m values vary from 0.5-0.81 in other systems. This indicates that the behavior of drug–surfactant mixed system is basically ruled by the strong tendency of nonionic surfactants to micellize. Tween 80 is more hydrophobic than Tween 40 and hence its contribution is more in mixed micelles than that of Tween 40. Similar is the case of P85 and F108. The mole fraction of surfactant in ideal mixed state (X_1^{id}) has been computed using equation (3.4). The values are greater than X_1^m, Tables 3.16 to 3.18, which indicate that the micelles are rich in drug.

The β^m values for all the systems (Tables 3.16 to 3.18) are negative suggesting that the attractive interaction between the drugs and nonionic surfactants is stronger than the individual components. The values of f_1^m and f_2^m , (Tables 3.16 to 3.18) are all less than unity, again confirming the non ideality in the mixed systems.

The stability of mixed micelles is confirmed by the negative value of excess free energy of mixing ΔG_{ex}° (Tables 3.16 to 3.18). All the negative ΔG_{ex}° values show that the drug-surfactant mixed micelles are more stable than the micelles of pure drugs.

Also all ΔG_m° are negative indicating that the process of micelle formation is spontaneous. For mixed systems, the magnitude of ΔG_m° increases with the increase in α_1. This is understandable as presence of surfactants in between the head groups of drugs reduces the electrostatic repulsion and makes the process more spontaneous.

The equation (3.10) used to calculate mole fraction of surfactants in mixed monolayer was non convergent for ADP- surfactant systems and also for some systems of NOT and CLP. Non convergence has been reported for other systems also [68-70].

X_1^{σ} values are always greater than X_1^{m} values (Tables 3.19 to 3.21). This means the participation of surfactants is more in monolayer formation than in micelle formation. The hydrophobicity of drug makes micelle formation more favorable with drugs and hence they participate more in micelle formation.

The values of interaction parameter, β^{σ} (Tables 3.19 to3.21), are negative except for NOT–P85 systems. The negative values indicate strong attractive interactions. The magnitudes of β^{σ} are greater than β^{m} values. The data are insufficient to draw any conclusion regarding nature of mixed monolayers. The values of f_1^{σ}, f_2^{σ} (Tables 3.19 to 3.21), are less than unity, indicating nonideal behavior in the mixed monolayer.

The Γ_{max} and A_{min} values are calculated by equations (3.13) and (3.14) with n = 1 for nonionic surfactants, n = 2 for pure drugs and n = 3 for mixtures. The values are given in Tables 3.19 to 3.21 (see Figs. 3.27 to 3.28). At α_1 = 0.0015, the Γ_{max} values in all systems show a sharp decrease. For greater α_1, Γ_{max} values increase slightly with increase in α_1. May be, at first addition, nonionic surfactant disturbs the surface and Γ_{max} decreases sharply. Also, with the addition of nonionic surfactants, drugs form mixed micelles with the surfactants and the monolayer will be loose. Similar trend of decrease and then increase was observed by Oida et al. [71] also. Values of A_{min} follow opposite order.

The values of G_{min}, calculated by equation (3.15) and listed in Tables 3.19 to 3.21, are found to decrease with increasing additive (nonionic surfactants) mole fraction. The lower the value of G_{min}, the more thermodynamically stable surface is formed.

The ΔG°_{ads} values are negative and are lower than ΔG°_{m}. The absolute values are more than double (and in some cases even greater) of ΔG°_{m}, indicating that the hydrophobicity of the components leads them towards the interface.

Table 3.15: *Variation of cmc and cmc* for mixed drug-nonionic surfactant systems.*

Mole fraction	ADP		NOT		CLP	
	cmc (mM)	*cmc** (mM)	*cmc* (mM)	*cmc** (mM)	*cmc* (mM)	*cmc** (mM)
0	41.0		20.8		18.48	
T40						
0.0015	8.86	12.71	4.39	9.77	3.69	9.20
0.003	5.94	7.52	3.16	6.39	2.00	6.15
0.0045	4.73	5.34	2.40	4.74	1.92	4.61
0.006	2.80	4.14	1.32	3.77	0.54	3.69
1	0.028					
T80						
0.0015	5.45	7.25	2.69	6.19	2.14	5.96
0.003	3.29	3.98	1.78	3.63	1.99	3.56
0.0045	2.24	2.74	1.08	2.57	1.56	2.53
0.006	1.54	2.09	0.92	1.99	0.83	1.97
1	0.013					
P85						
0.0015	15.12	19.16	6.97	13.19	5.17	12.22
0.003	10.8	9.27	4.73	7.61	4.56	7.27
0.0045	7.41	9.28	2.96	7.61	2.52	7.28
0.006	4.78	7.38	1.38	6.29	2.19	6.06
1	0.05					
F108						
0.0015	6.11	14.69	3.22	10.90	3.25	10.23
0.003	3.86	8.95	2.47	7.39	2.62	7.07
0.0045	3.16	6.43	1.66	5.59	1.59	5.40
0.006	2.89	5.02	0.86	4.49	0.83	4.37
1	0.034					

Table 3.16: *Various physicochemical parameters (i.e., X_1^m, X_1^{id}, β^m, f_1^m, f_2^m, ΔG_{ex}° and ΔG_m°) for mixed ADP–nonionic surfactant systems.*

Mole fraction	X_1^m	X_1^{id}	β^m	f_1^m	f_2^m	ΔG_{ex}° (kJ mol^{-1})	ΔG_m° (kJ mol^{-1})
0							-18.2
T40							
0.0015	0.61	0.69	-1.58	0.79	0.55	-0.9	-22.0
0.003	0.72	0.87	-1.31	0.90	0.51	-0.7	-23.0
0.0045	0.79	0.87	-0.88	0.97	0.57	-0.4	-23.6
0.006	0.73	0.89	-2.56	0.89	0.25	-1.3	-24.9
1							-36.6
T80							
0.0015	0.71	0.82	-1.57	0.87	0.45	-0.8	-23.2
0.003	0.79	0.90	-1.49	0.94	0.39	-0.6	-24.5
0.0045	0.81	0.93	-1.86	0.94	0.29	-0.7	-25.5
0.006	0.79	0.95	-2.76	0.89	0.18	-1.2	-26.4
1							-38.4
P85							
0.0015	0.52	0.53	-0.95	0.81	0.77	-0.6	-20.7
0.003	0.65	0.69	-0.67	0.92	0.75	-0.4	-21.5
0.0045	0.69	0.77	-1.14	0.90	0.58	-0.6	-22.5
0.006	0.68	0.82	-2.26	0.79	0.36	-1.2	-23.6
1							-34.9
F108							
0.0015	0.55	0.64	-3.62	0.48	0.33	-2.3	-23.0
0.003	0.61	0.78	-3.85	0.55	0.24	-2.3	-24.1
0.0045	0.65	0.84	-3.62	0.64	0.22	-2.1	-24.6
0.006	0.69	0.87	-3.16	0.74	0.22	-1.7	-24.8
1							-36.0

Table 3.17: *Various physicochemical parameters (i.e., X_1^m, X_1^{id}, β^m, f_1^m, f_2^m, ΔG_{ex}° and ΔG_m°) for mixed NOT–nonionic surfactant systems.*

Mole fraction	X_1^m	X_1^{id}	β^m	f_1^m	f_2^m	ΔG_{ex}° (kJ mol^{-1})	ΔG_m° (kJ mol^{-1})
0							-19.9
T40							
0.0015	0.512	0.531	-3.21	0.53	0.43	-2.0	-23.8
0.003	0.580	0.694	-3.09	0.63	0.35	-1.9	-24.7
0.0045	0.619	0.773	-3.16	0.57	0.30	-1.9	-25.3
0.006	0.609	0.820	-4.90	0.62	0.16	-2.9	-26.8
1							-36.6
T80							
0.0015	0.578	0.703	-3.58	0.47	0.30	-2.2	-25.0
0.003	0.639	0.826	-3.53	0.58	0.24	-2.0	-26.1
0.0045	0.649	0.877	-4.59	0.63	0.14	-2.6	-27.3
0.006	0.673	0.905	-4.45	0.47	0.13	-2.5	-27.7
1							-38.4
P85							
0.0015	0.443	0.367	-2.74	0.43	0.59	-1.7	-22.6
0.003	0.388	0.537	-2.86	0.51	0.47	-1.8	-23.6
0.0045	0.416	0.636	-3.88	0.45	0.31	-2.4	-24.8
0.006	0.459	0.700	-6.33	0.28	0.15	-3.9	-26.7
1							-34.9
F108							
0.0015	0.494	0.477	-4.90	0.29	0.30	-3.1	-24.6
0.003	0.546	0.646	-4.50	0.39	0.26	-2.8	-25.2
0.0045	0.570	0.733	-3.20	0.38	0.18	-3.2	-26.2
0.006	0.571	0.785	-7.25	0.26	0.09	-4.5	-27.9
1							-36.0

Table 3.18: *Various physicochemical parameters (i.e., X_1^m, X_1^{id}, β^m, f_1^m, f_2^m, ΔG_{ex}° and ΔG_m°) for mixed CLP–nonionic surfactant systems.*

Mole fraction	X_1^m	X_1^{id}	β^m	f_1^m	f_2^m	ΔG_{ex}° (kJ mol^{-1})	ΔG_m° (kJ mol^{-1})
0							-20.2
T40							
0.0015	0.50	0.50	-3.71	0.40	0.39	-2.3	-24.2
0.003	0.56	0.67	-4.81	0.39	0.22	-3.0	-25.8
0.0045	0.66	0.74	-4.00	0.52	0.24	-2.4	-25.9
0.006	0.57	0.79	-8.67	0.20	0.06	-5.4	-29.1
1							-36.5
T80							
0.0015	0.57	0.68	-4.37	0.44	0.25	-2.7	-25.6
0.003	0.65	0.81	-2.84	0.71	0.30	-1.6	-25.8
0.0045	0.70	0.86	-2.71	0.78	0.27	-1.4	-26.4
0.006	0.61	0.89	-4.71	0.58	0.13	-2.7	-28.0
1							-38.4
P85							
0.0015	0.45	0.34	-3.67	0.32	0.48	-2.3	-23.4
0.003	0.51	0.51	-2.93	0.49	0.47	-1.8	-23.7
0.0045	0.54	0.61	-4.41	0.39	0.28	-2.8	-25.2
0.006	0.56	0.67	-4.31	0.43	0.26	-2.7	-25.5
1							-34.9
F108							
0.0015	0.49	0.45	-4.72	.0.29	0.32	-2.9	-24.5
0.003	0.55	0.62	-4.14	0.42	0.29	-2.6	-25.1
0.0045	0.57	0.71	-5.39	0.40	0.17	-3.3	-26.3
0.006	0.57	0.77	-7.13	0.26	0.10	-4.4	-28.0
1							-36.0

Table 3.19: *Interfacial composition (X_1^σ), interaction parameter (β^σ), activity coefficients (f_i^σ) in mixed monolayer and surface properties (Γ_{max}, A_{min}, G_{min} and ΔG°_{ads}) for mixed ADP–nonionic surfactant systems.*

Mole fraction	X_1^σ	β^σ	f_1^σ	f_2^σ	$\Gamma_{max} \cdot 10^6$ (mol m^{-2})	A_{min} (Å^2)	G_{min} (kJ mol^{-1})	ΔG°_{ads} (kJ mol^{-1})
0					1.73	95.75	24.8	-34.6
T40								
0.0015					0.73	226.39	56.59	-63.6
0.003					0.78	213.72	52.84	-62.3
0.0045					0.78	211.72	50.37	-65.0
0.006					0.80	208.79	53.82	-59.8
1					2.51	66.23	15.20	-50.3
T80								
0.0015					0.62	265.84	71.73	-64.3
0.003					0.63	264.38	77.39	-60.9
0.0045					0.66	252.71	71.77	-62.2
0.006					0.70	238.11	68.55	-58.3
1					3.18	52.26	12.27	-48.2
P85								
0.0015					0.29	580.26	143.47	-123.1
0.003					0.35	470.01	105.73	-116.4
0.0045					0.38	431.53	97.21	-112.7
0.006					0.47	351.56	89.04	-86.7
1					1.23	134.96	28.08	-63.9
F108								
0.0015					0.34	495.15	131.67	-104.1
0.003					0.34	487.69	126.31	-107.7
0.0045					0.35	472.18	127.98	-97.6
0.006					0.60	227.64	66.05	-76.1
1					0.75	220.58	51.15	-79.1

Table 3.20: *Interfacial composition (X_1^σ), interaction parameter (β^σ), activity coefficients (f_i^σ) in mixed monolayer and surface properties (Γ_{max}, A_{min}, G_{min} and ΔG°_{ads}) for mixed NOT–nonionic surfactant systems.*

Mole fraction	X_1^σ	β^σ	f_1^σ	f_2^σ	$\Gamma_{max} \cdot 10^6$ (mol m^{-2})	A_{min} (Å^2)	G_{min} (kJ mol^{-1})	ΔG°_{ads} (kJ mol^{-1})
0					1.652	100.52	26.9	-36.5
T40								
0.0015	0.655	-1.217	0.87	0.59	0.720	230.62	60.4	-62.7
0.003					0.730	227.61	58.3	-63.7
0.0045					0.731	227.13	57.6	-66.2
0.006	0.703	-3.813	0.71	0.15	0.787	210.97	52.2	-63.5
1					2.506	66.23	15.2	-50.3
T80								
0.0015	0.633	-4.211	0.57	0.19	0.643	258.38	61.5	-72.5
0.003	0.699	-3.861	0.70	0.15	0.656	253.28	61.2	-73.9
0.0045	0.692	-5.133	0.61	0.09	0.694	239.21	55.9	-73.7
0.006	0.857	-1.759	0.96	0.27	0.713	232.89	59.1	-67.2
1					3.177	52.26	12.3	-48.2
P85								
0.0015	0.376	8.959	32.7	3.55	0.253	655.86	158.0	-141.1
0.003	0.180	6.139	62.1	1.22	0.282	588.76	139.9	-133.9
0.0045					0.292	569.47	133.8	-137.9
0.006					0.293	567.21	134.9	-130.9
1					1.230	134.95	28.1	-63.9
F108								
0.0015					0.322	516.37	136.8	-108.5
0.003					0.393	422.72	101.8	-105.6
0.0045					0.428	387.67	86.6	-104.6
0.006	0.702	-4.562	0.67	0.11	0.434	382.35	82.9	-106.2
1					0.753	220.58	51.1	-79.1

Table 3.21: *Interfacial composition (X_1^σ), interaction parameter (β^σ), activity coefficients (f_i^σ) in mixed monolayer and surface properties (Γ_{max}, A_{min}, G_{min} and ΔG°_{ads}) for mixed CLP–nonionic surfactant systems.*

Mole fraction	X_1^σ	β^σ	f_1^σ	f_2^σ	$\Gamma_{max} \cdot 10^6$ (mol m^{-2})	A_{min} (Å^2)	G_{min} (kJ mol^{-1})	ΔG°_{ads} (kJ mol^{-1})
0					1.61	103.11	24.8	-34.5
T 40								
0.0015	0.68	-3.95	0.67	0.16	0.68	244.32	66.9	-70.2
0.003					0.64	258.26	65.3	-59.7
0.0045	0.66	-7.01	0.44	0.05	0.72	230.55	60.5	-66.7
0.006					0.73	228.42	59.6	-59.7
1					2.51	66.23	15.2	-50.3
T 80								
0.0015	0.82	-0.69	0.98	0.63	0.69	241.13	67.6	-59.7
0.003	0.80	-2.11	0.92	0.26	0.70	238.50	61.8	-65.4
0.0045	0.72	-5.15	0.67	0.07	0.73	228.92	55.2	-68.7
0.006	0.69	-6.96	0.51	0.04	0.78	212.93	50.8	-68.3
1					3.18	52.26	12.3	-48.2
P85								
0.0015	0.61	-11.05	0.19	0.02	0.32	518.00	116.9	-131.0
0.003	0.77	-4.52	0.79	0.07	0.33.	506.80	122.1	-118.3
0.0045	0.70	-8.43	0.47	0.02	0.34	490.26	116.6	-115.2
0.006	0.64	-14.22	0.16	0.03	0.39	431.05	85.8	-124.1
1					1.23	134.95	28.1	-63.9
F108								
0.0015					0.32	521.8	138.3	-110.8
0.003					0.33	508.54	131.3	-112.5
0.0045					0.36	458.22	118.7	-105.9
0.006	0.83	-4.01	0.88	0.07	0.55	303.42	73.4	-82.5
1					0.75	220.58	51.2	-79.1

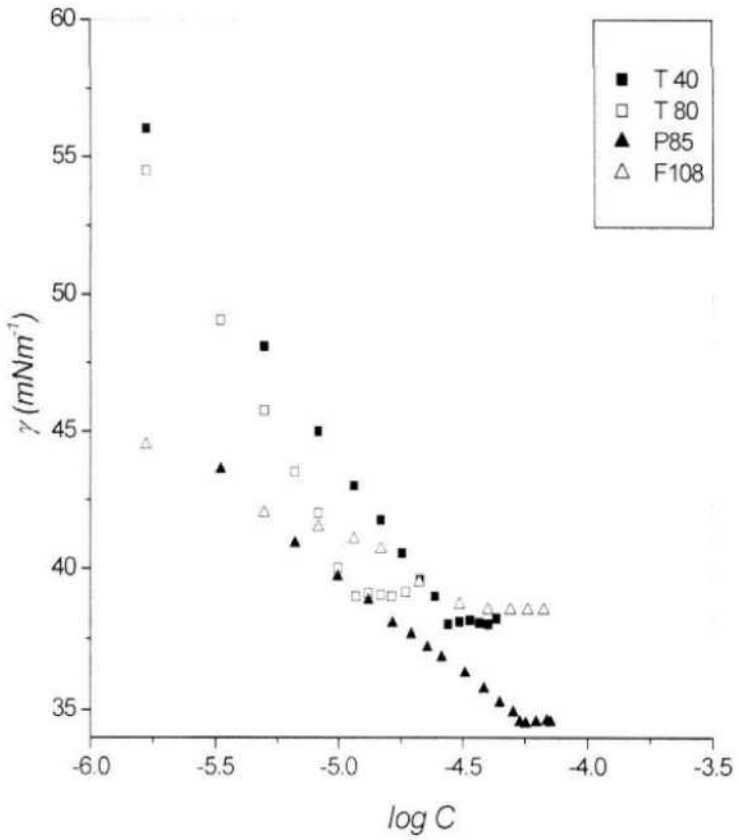


Fig. 3.22: *Plots of surface tension (γ) vs log C of pure nonionic surfactant (■ T 40, □ T 80, ▲ P85 and Δ F108).*

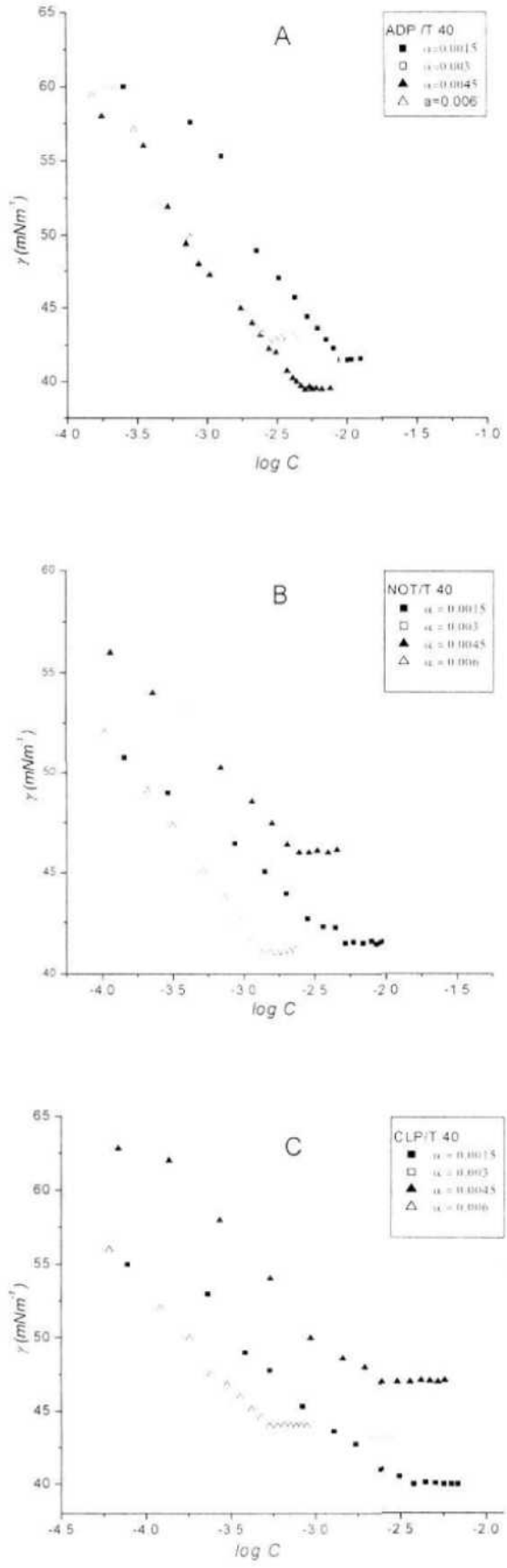


Fig. 3.23: *Plots of surface tension (γ) vs log C of T40 with ADP (A), NOT (B) and CLP (C) at different mole fractions of T40 (■ 0.0015, □ 0.003, ▲ 0.0045 and Δ 0.006).*

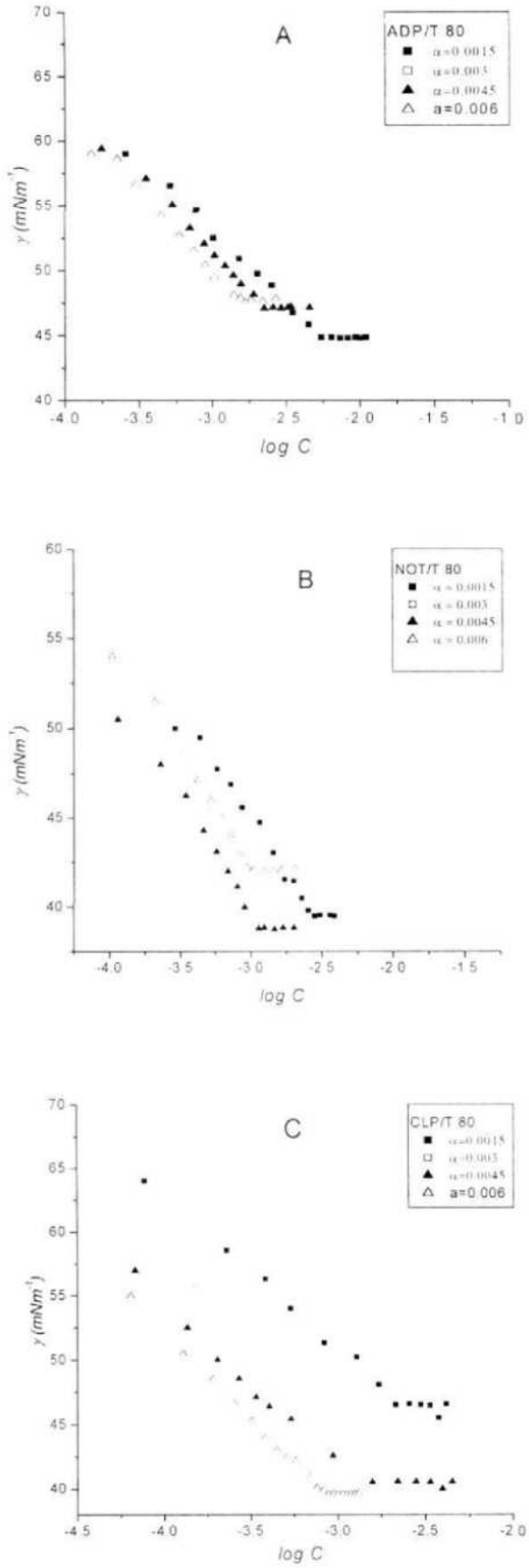


Fig. 3.24: *Plots of surface tension (γ) vs log C of T 80 with ADP (A), NOT (B) and CLP (C) at different mole fractions of T 80 (■ 0.0015, □ 0.003, ▲ 0.0045 and Δ 0.006).*

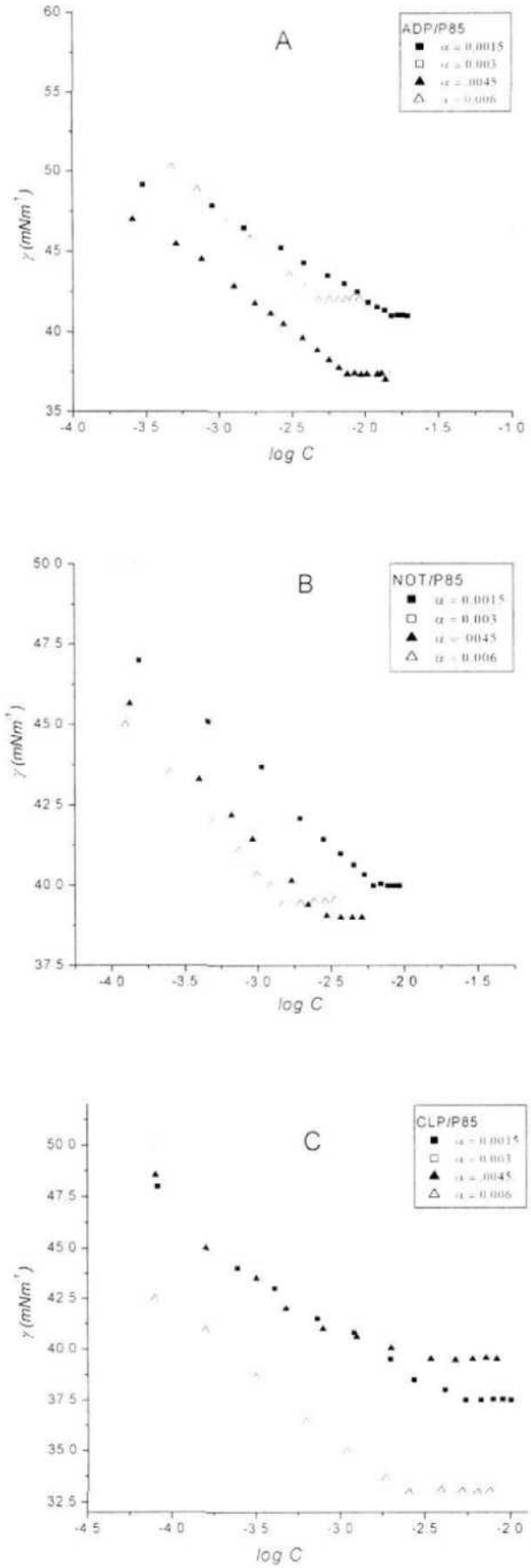


Fig. 3.25: *Plots of surface tension (γ) vs log C of P85 with ADP (A), NOT (B) and CLP (C) at different mole fractions of P85 (■ 0.0015, □ 0.003, ▲ 0.0045 and Δ 0.006).*

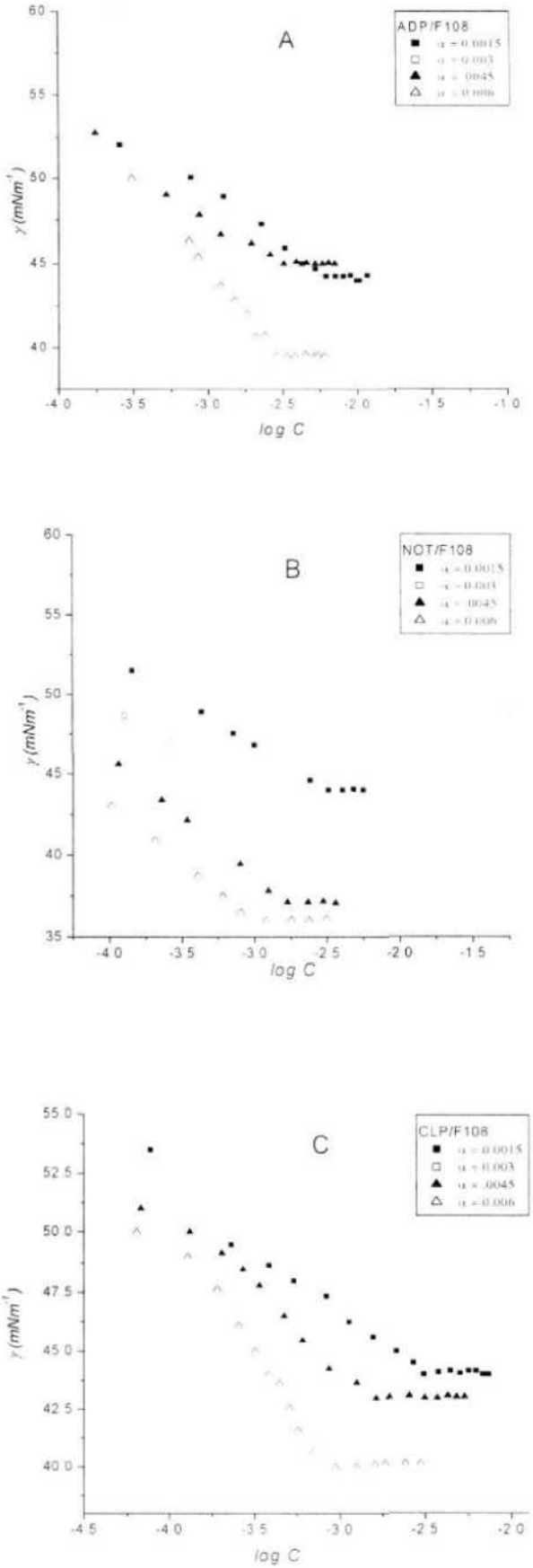


Fig. 3.26: *Plots of surface tension (γ) vs log C of F108 with ADP (A), NOT (B) and CLP (C) at different mole fractions of F108 (■ 0.0015, □ 0.003, ▲ 0.0045 and Δ 0.006).*

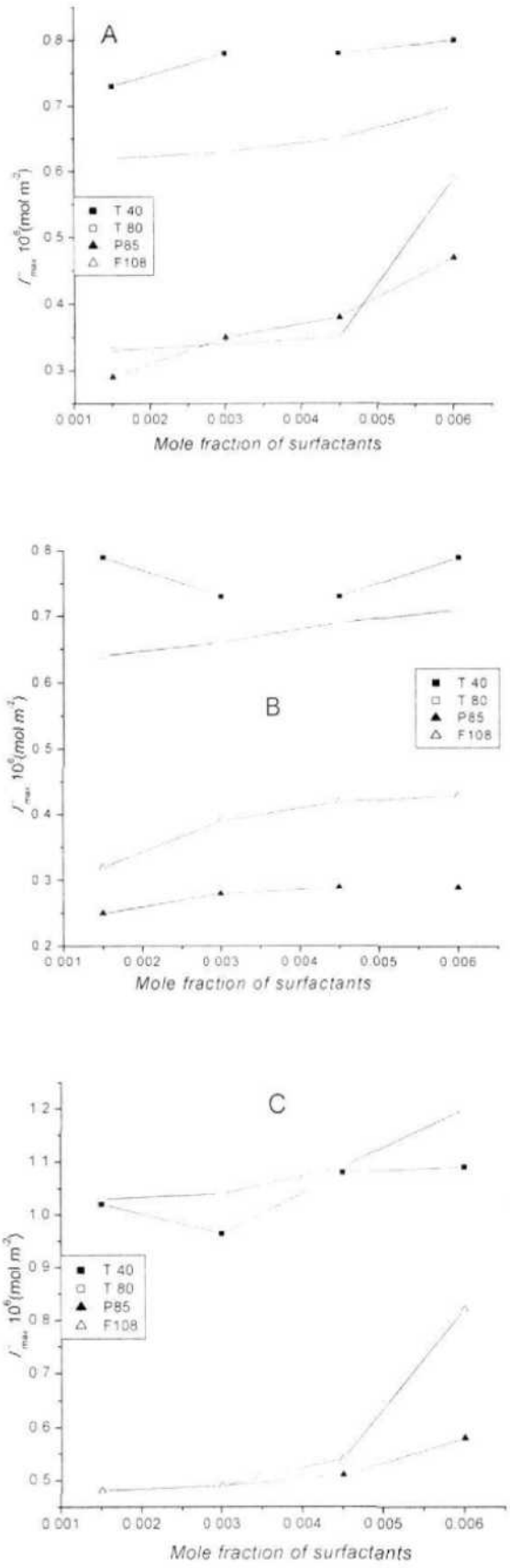


Fig. 3.27: *Variation of Γ_{max} with mole fraction of surfactants for ADP (A), NOT (B) and CLP (C) (■ T40, □ T 80, ▲ P85 and Δ F108).*

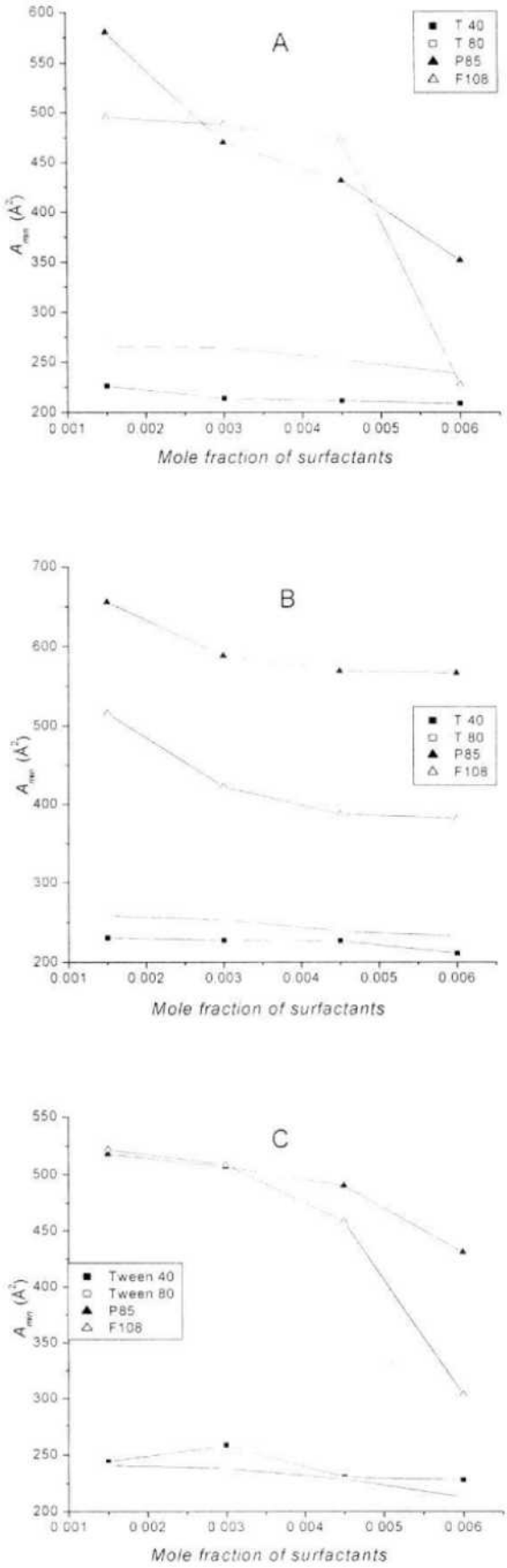


Fig. 3.28: *Variation of A_{min} with mole fraction of surfactants for ADP (A), NOT (B) and CLP (C) (■ T40, □ T80, ▲ P80 and Δ F108).*

(B) Drug – Salt Systems

In biological systems, growing of a bacterium is related to ion specificity [72]. The presence of an electrolyte in solution affects the behavior of amphiphiles which can be observed by studying the variation of *cmc* [73], aggregation number [74], morphological transitions/growth [75,76], dynamics of self-assembly [77,78], etc. Studies indicate that the ion specificity is a combination of various effects such as electrostatics, dispersion forces, thermal motion, hydrated ionic size, etc. [79-81]. The effect of different ions of same valency on the micellar properties of amphiphiles exemplifies the so-called Hofmeister effect.

There are several factors to decide the effect of salts on the structure and formation of micelles, such as chemical structure, nature (organic or inorganic), hydrated size of the counterions, etc. The effect of added salts on the micellization parameters has been attributed almost entirely to the counterion effect. Studies on surfactants have shown that the counterion exerts a strong influence on the *cmc*, aggregation number, size and shape of aggregates of ionic surfactant systems.

The inorganic salts affect the ionic surfactant solutions through electrostatic interactions. The inorganic salts are mainly considered as thickening agents for surfactant solutions. It is well known that the structure of the micelle is controlled by the hydrated size of the counterions for inorganic salts and the counterions with higher hydrophilicity prefer to stay in the bulk of micellar solution and therefore, are less effective to screen the charge on the micellar surface.

Hydrotropes are another class of amphiphiles that become weakly surface active at high concentrations. They generally contain a benzene ring with or without an attached substituent group as hydrophobic moiety. This moiety is still smaller than that of drugs and, hence, the *cmc* values, which are also known as minimum hydrotropes concentration (*mhc*) for hydrotropes, are higher than those of drugs and surfactants. This *mhc* coincides with the change in slope of the plot of surface tension and log of hydrotrope concentration [82]. Hydrotropes have many practical applications which include separation processes [83], increase of cloud point [84], change in reaction rates [85], and use in pharmaceutical formulations [86, 87]. For example, sodium salicylate has been found to increase the solubility of temazepam [88]. Similarly, sodium salicylate and sodium benzoate are known to increase the solubility of diazepam in different solvents [89].

It is a well known fact that the solution properties of amphiphiles change drastically upon addition of another amphiphile. In a number of cases, synergism takes place and, as a result, both surface tension and *cmc* decrease significantly [90-92]. Combining different amphiphiles thus widens the scope of producing a system with properties required for a particular application. With all these points in mind, we performed experiments on mixed systems of amphiphilic drugs and anionic hydrotropes at different stoichiometric mole fractions of hydrotropes. These hydrotropes, as mentioned in the preceding paragraph, are used in pharmaceutical formulations. Their use would reduce the undesirable effects of

drugs as well as the risk of precipitation of drug on its transition from liquid formulation to aqueous blood phase.

Results and Discussion

Addition of inorganic salts (NaCl, NaBr, KCl and KBr) as well as hydrotropes (NaSal, NaBenz and NaTos) decreases the *cmc* of the drugs. Figs. 3.29 to 3.36 depict the variation of *cmc* values of the three drugs with the concentration of added salts.

Condensation of counterions at the positively charged drug head groups decreases the electrostatic repulsion among them and *cmc* values decrease. Two mechanisms have been proposed for ions, behavior in micellar systems: in one mechanism ions directly adsorb or desorb on the micellar surface and in another, ions affect the solvent property of water [93,94]. However, in general, it is proposed that kosmotropic ions (or structure-maker ions which exhibit strong interactions with water) bind less strongly to the micellar surface than chaotropic ions (or structure-breaker ions which exhibit weak interactions with water). Chaotropic ions are less hydrated and promote micellization and micellar growth [95,96]. Thus, an increase in hydrophobicity of the counterion increases the amphiphiles' tendency to micellize and result in *cmc* lowering.

The *cmc* values in NaCl are slightly different from the values in presence of KCl, whereas the values in presence of NaBr are not very different from those with KBr. The reason for this is that Na^+/K^+ ions are coions for the cationic drug

micelles. However, slightly different values are due to the nature of these ions: these ions remain in aqueous phase and also affect the water structure. Hydrated radius of Na^+ ion is greater than that of K^+ ion (r_H for Na^+ ion is 3.82 Å and for K^+ ion is 3.31 Å) [97]. Therefore, Na^+ reduces the availability of water in the head group region more than K^+ ion. This increases the repulsions among the similar charged head groups. Hence, micellization becomes less favorable and reduction in *cmc* should be slower with Na^+ than with K^+. This indeed is observed in the present case.

Change in counterion has greater effect on *cmc* of the drugs. As Cl^- (r_h = 3.30 Å) is more hydrated than Br^-(r_h = 3.32 Å) , the latter interacts more strongly with the cationic drug micelles, causing greater shielding of positive charge; this decreases the electrostatic repulsions more as compared to Cl^-. Therefore, *cmc* decrease is more with Br^- than with Cl^- (Figs. 3.29 to 3.32, Table 3.22). The effect of organic salts including sodium benzoate, sodium salicylate and sodium tosylate with an aromatic phenyl group the so called hydrotropes, has also been studied with amphiphilic drug systems. The organic salts may influence the morphology of micelles in a manner that depends upon the extent of their penetration into the micelles. The NaSal, NaBenz and NaTos decrease the *cmc* values and greatly enhance the tight packing of the cationic drugs at air-water interface. The self-aggregation of drug micelles in presence of organic salts is the resultant of both the electrostatic and hydrophobic interactions. In the absence of

salts, the charges on the drug head groups keep the drug molecules away from each other by means of electrostatic repulsion. Salts are added to screen the effective charges in the head group. Aromatic counterions have strong tendency to penetrate the head group region and thus there is micellar growth at lower loading of the micellar surface as compared to weakly penetrating inorganic counterions. Generally, it is found that the *cmc* values decrease with increase in the concentration of the aromatic salts. The anion with more hydrophobic skeleton among organic salts gives rise to considerably lower *cmc's*. Thus, the properties of aqueous solution of cationic drugs can be efficiently modified by the addition of salts, especially organic salts and large-sized inorganic salts.

Representative plots of surface tension vs. log concentration for pure hydrotropes and for mixed systems (hydrotropes + drugs) at different mole fractions of hydrotropes are shown in Figs. 3.33 to 3.36. The variation of *cmc* and *cmc** for these mixed systems at different mole fractions of hydrotropes are recorded in Table 3.23. Regarding hydrotropes, the order of *cmc* is NaSal (528 mM) > NaBenz (382 mM) > NaTos (253 mM). NaBenz contains a carboxylate group; NaSal contains an additional OH group whereas NaTos has a sulphonate group and a CH_3 group. Hence, NaTos should be least hydrophilic and NaSal should be most hydrophilic among the three hydrotropes. Order of the *cmc* values confirms this. NaSal, the most hydrophilic one, forms aggregates at highest concentration. The *cmc* values of the mixture are lower than the *cmc* values of both drug and hydrotropes and decrease with the increase in stoichiometric mole

fractions (α_1) of the hydrotropes. The mixed micelles are formed due to synergistic interactions. The hydrotropes are in anionic form in aqueous media while drugs are in cationic form. Hence the systems show strong attractive interactions with the hydrotropes intercalating between the drug monomers [98,99]. This reduces the interhead group repulsions. Also the phenyl ring of the hydrotropes interacts with the ring part of the drug, strengthening the hydrophobic interactions. Hence *cmc* decreases. The decrease in *cmc* is maximum in NaBenz–drug systems. For drug–NaTos system the values are close to NaBenz system, whereas for drug–NaSal system the values are slightly higher. The difference in *cmc** and experimentally obtained cmc *(cmc)* gives an idea about the nature of the mixed system. The values of *cmc** in our case are always higher than the *cmc* values which means that the mixed micelles are formed due to attractive interactions among the two components.

The variation of *cmc*, *cmc**, Γ_{max}, A_{min}, ΔG^{o}_{m} and ΔG^{o}_{ads} are given in Tables 3.22 and 3.23.

The adsorption efficiency at air/water interface of these drugs and effect of electrolytes on adsorption can be assessed in the light of the Gibbs adsorption equation (3.13). The variable *n* is introduced to allow for simultaneous adsorption of cations and anions. *n* is calculated by the equation proposed by Matejevic and Pethica [100]: $n = 1 + m/(m + m_s)$, where m and m_s are the concentrations of amphiphile and electrolyte, respectively. Thus $n = 2$ in water and approaches 1 in the presence of excess inert electrolyte. The $dy/d\log C$ factor was obtained from the

slope of the linear part of γ vs. log C isotherms. Γ_{max} values were used to calculate minimum surface area per molecule, A_{min}, at the air/solution interface using the equation (3.14).

The values of Γ_{max} and A_{min} are given in Tables 3.22 and 3.23. We can see that Γ_{max} increases with the addition of salt. In general, the drugs positive ions in the micelle would attract counterions in order to compensate the headgroup coulombic repulsion, making the micelle as well as the monolayer formed stable and compact. Hence, Γ_{max} increases. Among Cl^- and Br^- ions, as Br^- ion is less hydrated than Cl^- ion, it affects the headgroup region more and the Γ_{max} is more in its presence. Change in coion (i.e., Na^+ or K^+) is relatively ineffective. As A_{min} values are inverse of Γ_{max} values, the behavior of A_{min} is self-explanatory in the light of the discussion for Γ_{max}.

The evaluated values of Γ_{max} for drug–hydrotrope surfactant systems is given in Table 3.23. As is clear from the data in the Table, the value for drug–hydrotrope mixtures increases with increases in α_1. Figs. 3.37 to 3.38 show the values of Γ_{max} and A_{min}. As A_{min} is inversely related to Γ_{max}, the decreasing trend is as expected. Both the components are oppositely charged and hence their mixing results in densely packed surface due to reduction in head group repulsions. That is why Γ_{max} increases and A_{min} decreases, the two components can come closer to each other in comparison to individual components. However, two points need to be discussed: (i) the value of Γ_{max} decreases with the first addition, i.e., at lowest

α_1 taken and (ii) the values are, in general, lower than Γ_{max} of pure components or in other words, A_{min} first increases at α_1 = 0.012 and then decreases and A_{min} is higher than that of pure components. As structures of both components are dissimilar, addition of hydrotrope (in small quantity) disturbs the molecular arrangement at the interface. Hence, molecules move slightly apart from each other. As a result, A_{min} increases (or Γ_{max} decreases). However, as more and more hydrotrotopes are added (i.e. higher α_1 values) the interaction among the two components dominates and molecules again come closer. However, the Γ_{max} (or A_{min}) values always remain lower (or higher) than those of pure components. Presence of hydrotrope decreases the repulsion among two drug molecules by intercalating between drug molecules and should decrease the A_{min}. But presence of hydrotrope at the interface increases the area as it also occupies some area. Similar expansion in minimum area was observed by other workers also [101, 102].

Values of molar free energy at the maximum adsorption attained at *cmc*, G_{min} [26] are also given in Table 3.23. It is the work required to make an interface per mole. The lower the value of G_{min}, the more stable surface is formed. The values of G_{min} decrease with increase in α_1 which supports our assertion that addition of hydrotropes makes the system more stable.

All the negative ΔG°_{ads} values for inorganic salts which were calculated using equation (3.16) and listed in Table 3.22 imply that the adsorption of the

amphiphilic molecules at the air/water interface take place spontaneously. The standard Gibbs energy of micellization, ΔG_m°, was evaluated using the equation (3.8). The ΔG_m° (Table 3.22) values are all negative suggesting the process of micellization to be spontaneous. The absolute values increase with the increase in concentration of added salts. As already explained, presence of the salt ions decreases the repulsions among head groups. This, in turn, decreases the factor opposing the process of micellization and micelle formation becomes easier.

The magnitude of (ΔG_m°) is lower for hydrotropes than for drugs (Table 3.23). The values for drug-hydrotrope systems are closer to that of drugs. The magnitudes are larger than that of drugs. This again confirm the order of systems stability as hydrotropes < drugs < drug–hydrotropes. ΔG_m° is greater in CLP–hydrotrope systems. The ΔG_m° values can be used to calculate the standard Gibbs energy of adsorption (ΔG_{ads}°) through equation (3.16), where the second term on right hand side of this equation is the work involved in going from zero surface pressure to surface potential at *cmc* at constant Γ_{max} value. These values too are negative and lower than ΔG_{ads}° (the ratio of ΔG_{ads}° to ΔG_m° is greater than 1.5, Table 3.23). This indicates that the molecule's hydrophobicity leads them toward the air/solution interface and only after its saturation micelle formation takes place.

As discussed earlier, hydrotropes have additional hydrophobic interactions beside electrostatic one, which leads to the formation of more stable mixed systems with cationic drugs due to synergistic interactions. Thus, a mixture

of hydrotropes with cationic drugs leads to the formation of mixed aggregates because of the different surface activity of the components.

Mixed micelles formed in the solution of such non homogenous surface active materials are expected to be nonideal. The nonideal mixing is quantified on the basis the regular solution theory (RST) as already discussed earlier.

The X_1^m values (Tables 3.24 to 3.26), calculated using equation (3.2) increase with increasing α_1 and the trend is: NaSal < NaBenz ≈ NaTos. Due to the hydrophilic nature, NaSal participates less in mixed micelle formation in comparison to NaBenz or NaTos. On the other hand, the X_1^{id} values increase with increasing content of hydrotropes in solution. However, the values are smaller than both α_1 and X_1^m. Ideally, the mixed micelles should contain only drug as drugs are hydrophobic and their molecules would form aggregates readily. As hydrotropes are also slightly amphiphilic in nature they also contribute in micelle formation increasing the aggregates hydrophobicity making mixed micelles more stable. The β^m values are negative for all systems and their large magnitudes suggest strong synergism in the mixed systems. The β_{av}^m values follow a trend similar to β_{av}^σ. For ADP–hydrotrope and NOT– hydrotrope systems, the values are almost equal, whereas, for CLP–hydrotropes the value changes from ~ -9 to ~ -15/-14 β^m values, (see Tables 3.24 to 3.26). These values suggest that although the hydrotropes are taking only little part in mixed micellization, due to their anionic nature, they interact strongly with the cationic drug molecules. Values of

f_1^m and f_2^m (activity coefficients of hydrotropes and drugs) indicate that hydrotorpes are far from their standard state while drugs are very close to standard state.

The excess free energy of micellization (ΔG_{ex}°) values are also negative and the magnitude increases with the increasing content of hydrotrope in the solution. This indicates that hydrotrope addition increases the hydrophobic interactions and makes the mixed micelles more stable than the micelles of individual components. The value of ΔG_{ex}° is greater in case of CLP–hydrotrope systems.

The interactions among the two mixed components can be analyzed using Rosen's mode [12]. This model gives mole fraction of one component in mixed monolayer (X_1^{σ}) as well as the nature and strength of interactions. If the interaction parameter, β^{σ}, comes out to be equal to zero, the interaction among the two components is taken as zero, that is the mixing is ideal. Negative β^{σ} values indicate attractive while positive values mean repulsive interactions.

The values of X_1^{σ} (Tables 3.24 to 3.26) increase with increasing α_1 value. This means that the two components are forming mixed micelles with increasing content of hydrotrope. In ADP–hydrotrope and NOT–hydrotrope systems, X_1^{σ} value shows no definite trend and vary slightly with salt type. However, in CLP–hydrotrope systems, X_1^{σ} values are in the order of NaSal < NaBenz < NaTos. As NaTos is most hydrophobic among the salts used, it tries to penetrate the drug

micelles and forms mixed micelles more readily than NaSal (which is most hydrophilic). The β^{σ} values calculated using X_1^{σ} values, come out to be negative. Average β^{σ} values are almost equal for the three ADP–hydrotrope and NOT–hydrotrope systems. For CLP–hydrotrope systems, the magnitude of β_{av}^{σ} varies in the order: NaSal < NaTos < NaBenz. With cationic surfactants (both conventional and gemini) NaSal have been found to interact most strongly [98, 99]. It was proposed in those studies that Sal^- ions intercalate between the surfactant head groups in such a way that COO^- group of one micelle interacts with the head groups of another micelle and thus form a chain of micelles. As the drugs are also cationic, we expect the interaction in drug–NaSal systems to be strongest. However, we obtained opposite results; NaSal is interacting weakly (comparatively) with these drugs. Probably the rigid and short hydrophobic parts of the drugs experience steric repulsion with the short ring structure of the hydrotropes.

Values of activity coefficients f_1^{σ} and f_2^{σ} of the two components at the interface can be seen in Tables 3.24 to 3.26. It is evident that these values are less than unity indicating nonideality in the solution. The values of f_1^{σ} (the activity coefficient of hydrotropes) are very low which suggest that hydrotropes are far away from their standard state in mixed micelles whereas drugs are comparatively much closer to this state (f_2^{σ} are greater than f_1^{σ} and in some systems are close to 1)

Table 3.22: *Values of cmc, Γ_{max} , A_{min} , ΔG_m^o, ΔG_{ads}^o for drugs- inorganic salts systems.*

Additive (mM)	*cmc* (mM)	$\Gamma_{max}.10^6$ (mol m^{-2})	A_{min} ($Å^2$)	ΔG_m^o (kJ mol^{-1})	ΔG_{ads}^o (kJ mol^{-1})
ADP/NaCl					
0	41.0	1.734	95.75	-18.2	-34.6
50	33.75	2.249	73.87	-18.7	-32.0
100	30.78	2.261	73.36	-18.9	-32.9
150	28.40	2.277	72.75	-19.1	-34.2
200	25.70	2.289	72.36	-19.3	-33.1
ADP/KCl					
50	31.99	2.348	70.63	-18.8	-32.1
100	28.84	2.391	69.55	-19.0	-32.4
150	27.75	2.405	69.23	-19.1	-33.3
200	25.02	2.413	68.93	-19.4	-34.0
ADP/NaBr					
50	29.74	2.524	65.81	-18.9	-32.5
100	26.61	2.539	65.27	-19.2	-32.6
150	24.74	2.573	64.53	-19.4	-32.9
200	22.82	2.602	63.88	-19.6	-33.0
ADP/KBr					
50	28.18	2.645	62.99	-19.1	-31.9
100	25.31	2.653	62.61	-19.4	-32.2
150	23.62	2.669	62.08	-19.5	-32.3
200	20.11	2.692	61.63	-19.9	-32.5
NOT/NaCl					
0	20.8 0	1.652	100.52	-19.9	-36.5
50	16.53	2.160	77.92	-20.6	-35.0
100	15.02	2.162	76.77	-20.7	-35.0
150	12.35	2.199	75.49	-21.2	-36.2
200	9.36	2.219	74.83	-21.9	-37.2

NOT/KCl					
50	15.80	2.258	73.52	-20.6	-34.7
100	15.50	2.292	72.43	-20.6	-34.6
150	12.06	2.305	72.04	-21.3	-35.5
200	9.13	2.311	71.84	-21.9	-36.7
NOT/NaBr					
25	18.65	2.547	65.18	-20.2	-32.1
50	14.02	2.586	64.27	-20.9	-33.8
100	12.77	2.587	64.17	-21.1	-34.5
NOT/KBr					
25	16.34	2.631	63.11	-20.5	-33.2
50	15.37	2.633	63.07	-20.6	-34.3
100	11.78	2.653	62.59	-21.3	-34.9
CLP/NaCl					
0	18.48	1.610	103.11	-20.2	-34.5
50	12.28	2.014	82.44	-21.2	-37.1
100	10.21	2.042	81.30	-21.7	-37.7
150	9.24	2.103	78.93	-22.9	-37.9
200	6.51	2.111	78.64	-22.8	-38.9
CLP/KCl					
50	11.68	2.143	77.47	-21.3	-36.5
100	10.20	2.184	76.03	-21.7	-37.2
150	7.98	2.203	75.36	-22.3	-37.5
200	5.26	2.248	73.86	-23.3	-38.7
CLP/NaBr					
25	13.89	2.567	64.62	-20.9	-34.4
50	9.47	2.593	64.04	-21.9	-35.5

Table 3.23: *Values of cmc, cmc*, Γ_{max}, A_{min}, ΔG_m^o, ΔG^o_{ads}, and G_{min} for drugs-hydrotropic surfactant systems*

Mole fraction	*cmc* (mM)	*cmc** (mM)	$\Gamma_{max}.10^6$ (mol m^{-2})	A_{min} ($Å^2$)	ΔG_m^o (kJ mol^{-1})	ΔG_{ads}^o (kJ mol^{-1})	G_{min} (kJ mol^{-1})
ADP/NaSal							
0	41		1.734	95.75	-18.2	-34.6	24.8
0.012	34.38	41.45	1.692	98.13	-18.6	-32.4	28.4
0.024	26.75	41.93	1.716	96.74	-19.3	-34.4	25.7
0.036	23.86	42.40	1.893	89.74	-19.6	-34.7	23.7
0.048	16.66	42.89	1.875	88.54	-20.4	-33.1	24.3
1	528		1.761	94.30	-11.8	-24.8	26.9
ADP/NaBenz							
0.012	36.60	41.44	1.378	120.43	-18.5	-34.4	35.2
0.024	30.80	41.89	1.364	121.68	-18.9	-33.7	36.6
0.036	17.18	42.36	1.392	119.25	-19.3	-36.6	34.7
0.048	9.02	42.83	1.403	118.38	-22.0	-40.0	32.1
1	382		1.518	109.35	-12.6	-23.4	35.4
ADP/NaTos							
0.012	33.96	41.41	1.409	117.86	-18.6	-34.7	33.7
0.024	29.45	41.83	1.491	111.36	-19.0	-35.3	32.0
0.036	15.73	42.26	1.549	107.18	-20.6	-36.8	30.3
0.048	13.18	42.72	1.681	98.79	-21.0	-35.8	27.4
1	253		1.861	89.23	-13.8	-27.7	23.9
NOT/NaSal							
0	20.80		1.652	100.25	-19.9	-36.5	26.9
0.012	18.39	21.04	0.944	175.81	-20.2	-52.2	42.5
0.024	14.79	21.29	1.068	155.42	-20.7	-53.2	34.2
0.036	12.49	21.55	1.176	141.13	-21.2	-47.3	34.0
0.048	9.55	21.81	1.208	137.44	-21.9	-43.4	36.4
1	528		1.761	94.30	-11.8	-24.8	26.9
NOT/NaBenz							
0.012	18.00	21.04	0.869	191.12	-20.2	-48.3	52.4
0.024	15.04	21.28	1.154	143.83	-20.7	-43.3	38.3
0.036	12.46	21.53	1.157	143.44	-21.2	-40.1	42.4
0.048	8.19	12.79	1.539	107.87	-22.2	-39.5	29.6
1	382		1.518	109.35	-12.6	-23.4	35.4

NOT/NaTos							
0.012	17.63	21.03	1.256	132.18	-20.3	-45.1	31.1
0.024	13.49	21.27	1.165	142.53	-21.0	-51.8	31.9
0.036	12.15	21.51	1.159	143.24	-21.3	-51.0	32.4
0.048	9.54	21.75	1.434	115.75	-21.9	-47.4	25.2
1	253		1.861	89.23	-13.8	-27.7	23.9
CLP/NaSal							
0	18.48		1.610	103.10	-20.2	-34.5	29.2
0.012	14.70	18.70	0.464	357.74	-20.8	-70.3	99.3
0.024	12.28	18.92	0.486	341.71	-21.2	-70.6	95.7
0.036	9.39	19.15	0.489	339.40	-21.9	-73.1	95.0
0.048	7.58	19.38	0.509	326.05	-22.4	-70.5	93.3
1	528		1.761	94.30	-11.8	-24.8	26.9
CLP/NaBenz							
0.012	5.27	18.69	0.459	361.42	-23.4	-68.0	110.5
0.024	3.15	18.91	0.629	263.90	-24.6	-63.5	74.2
0.036	2.66	19.14	0.645	257.21	-25.1	-64.6	70.5
0.048	1.93	17.37	0.780	212.83	-25.9	-57.3	60.9
1	382		1.518	109.35	-12.6	-23.4	35.4
CLP/NaTos							
0.012	5.91	18.69	0.442	375.94	-23.0	-82.3	103.0
0.024	4.22	18.90	0.527	315.15	-23.9	-75.7	84.4
0.036	3.96	19.11	0.532	311.91	-24.1	-71.8	85.7
0.048	1.86	19.34	0.860	193.10	-26.0	-63.1	46.5
1	253		1.861	89.23	-13.8	-27.7	23.9

Table 3.24: *Various physicochemical parameters (X_1^m , X_1^{id} , β^m , f_1^m , f_2^m , ΔG_{ex}^{o} , X_1^{σ} , β^{σ} , f_1^{σ} and f_2^{σ}) for ADP– hydrotropic surfactant systems.*

Mole Fraction	X_1^m	X_1^{id}	β^m	f_1^m	f_2^m	ΔG_{ex}^{o} (kJ mol^{-1})	X_1^{σ}	β^{σ}	f_1^{σ}	f_2^{σ}
NaSal										
0.012	0.109	0.001	-6.2	0.007	0.93	-1.5				
0.024	0.183	0.002	-7.5	0.007	0.78	-2.8	0.17	-7.6	0.005	0.80
0.036	0.210	0.003	-7.8	0.008	0.71	-3.3	0.19	-7.8	0.005	0.74
0.048	0.262	0.004	-9.5	0.006	0.52	-4.6	0.23	-8.6	0.006	0.63
NaBenz										
0.012	0.089	0.002	-5.1	0.013	0.96	-1.0	0.14	-7.9	0.003	0.86
0.024	0.154	0.003	-6.1	0.013	0.87	-2.2	0.11	-6.2	0.010	0.93
0.036	0.258	0.004	-9.2	0.005	0.57	-4.4	0.12	-5.8	0.010	0.93
0.048	0.315	0.005	-9.9	0.004	0.31	-6.5	0.29	-12.5	0.002	0.36
NaTos										
0.012	0.118	0.002	-5.4	0.015	0.93	-1.4				
0.024	0.170	0.004	-5.8	0.018	0.84	-2.1				
0.036	0.275	0.007	-8.9	0.009	0.51	-4.5	0.21	-6.6	0.02	0.75
0.048	0.298	0.009	-9.6	0.009	0.43	-5.0	0.27	-8.4	0.79	0.54

Table 3.25: *Various physicochemical parameters (X_1^m , X_1^{id} , β^m , f_1^m , f_2^m , ΔG_{ex}° , X_1^{σ}, β^{σ}, f_1^{σ} and f_2^{σ}) for NOT– hydrotropic surfactant systems.*

Mole fraction	X_1^m	X_1^{id}	β^m	f_1^m	f_2^m	ΔG_{ex}° (kJ mol^{-1})	X_1^{σ}	β^{σ}	f_1^{σ}	f_2^{σ}
NaSal										
0.012	0.086	0.0005	-6.36	0.005	0.95	-1.3	0.25	-13.55	0.0004	0.43
0.024	0.158	0.0010	-7.71	0.004	0.82	-2.6	0.30	-15.99	0.0004	0.23
0.036	0.197	0.0015	-8.44	0.004	0.72	-3.4	0.26	-12.30	0.0040	0.43
0.048	0.239	0.0020	-9.72	0.004	0.57	-4.5	0.25	-10.55	0.0025	0.52
NaBenz										
0.012	0.095	0.0007	-6.26	0.006	0.94	-1.4	0.01	-3.12	0.046	0.99
0.024	0.158	0.0013	-7.22	0.006	0.84	-2.5	0.16	-8.75	0.002	0.79
0.036	0.201	0.0020	-8.06	0.006	0.72	-3.3	0.18	-8.79	0.003	0.75
0.048	0.260	0.0027	-10.1	0.004	0.51	-4.9	0.24	-10.82	0.002	0.54
NaTos										
0.012	0.105	0.0011	-5.95	0.009	0.94	-1.4	0.28	-13.64	0.001	0.33
0.024	0.186	0.0022	-7.40	0.007	0.77	-2.8	0.31	-13.63	0.001	0.26
0.036	0.211	0.0033	-7.60	0007	0.71	-3.2	0.32	-14.42	0.002	0.21
0.048	0.251	0.0044	-8.65	0.009	0.58	-4.1	0.33	-13.87	0.002	0.22

Table 3.26: *Various physicochemical parameters (X_1^m , X_1^{id} , β^m , f_1^m , f_2^m , ΔG_{ex}^o , X_1^σ , β^σ , f_1^σ and f_2^σ) for CLP– hydrotropic surfactant systems.*

Mole fraction	X_1^m	X_1^{id}	β^m	f_1^m	f_2^m	ΔG_{ex}^o (kJ mol^{-1})	X_1^σ	β^σ	f_1^σ	f_2^σ
NaSal										
0.012	0.12	0.0004	-7.65	0.003	0.89	-2.1	0.08	-6.08	0.006	0.97
0.024	0.17	0.0009	-8.29	0.003	0.79	-3.0	0.13	-6.81	0.006	0.89
0.036	0.22	0.0013	-9.63	0.003	0.62	-4.2	0.16	-7.14	0.006	0.83
0.048	0.25	0.0018	-10.48	0.003	0.92	-5.0	0.24	-9.72	0.004	0.57
NaBenz										
0.012	0.27	0.0006	-13.88	0.001	0.36	-6.9				
0.024	0.31	0.0012	-15.45	0.001	0.23	-8.3	0.28	-14.43	0.001	0.32
0.036	0.33	0.0018	-15.73	0.001	0.21	-8.7	0.32	-16.90	0.001	0.18
0.048	0.34	0.0024	-16.63	0.001	0.15	-9.4	0.32	-16.16	0.001	0.19
NaTos										
0.012	0.27	0.0010	-12.42	0.001	0.42	-6.2	0.27	-12.15	0.002	0.41
0.024	0.30	0.0019	-13.30	0.001	0.30	-7.1	0.33	-15.10	0.001	0.19
0.036	0.31	0.0029	-13.09	0.002	0.28	-7.1	0.32	-13.11	0.002	0.26
0.048	0.35	0.0039	-16.21	0.001	0.14	-9.3	0.34	-14.10	0.002	0.20

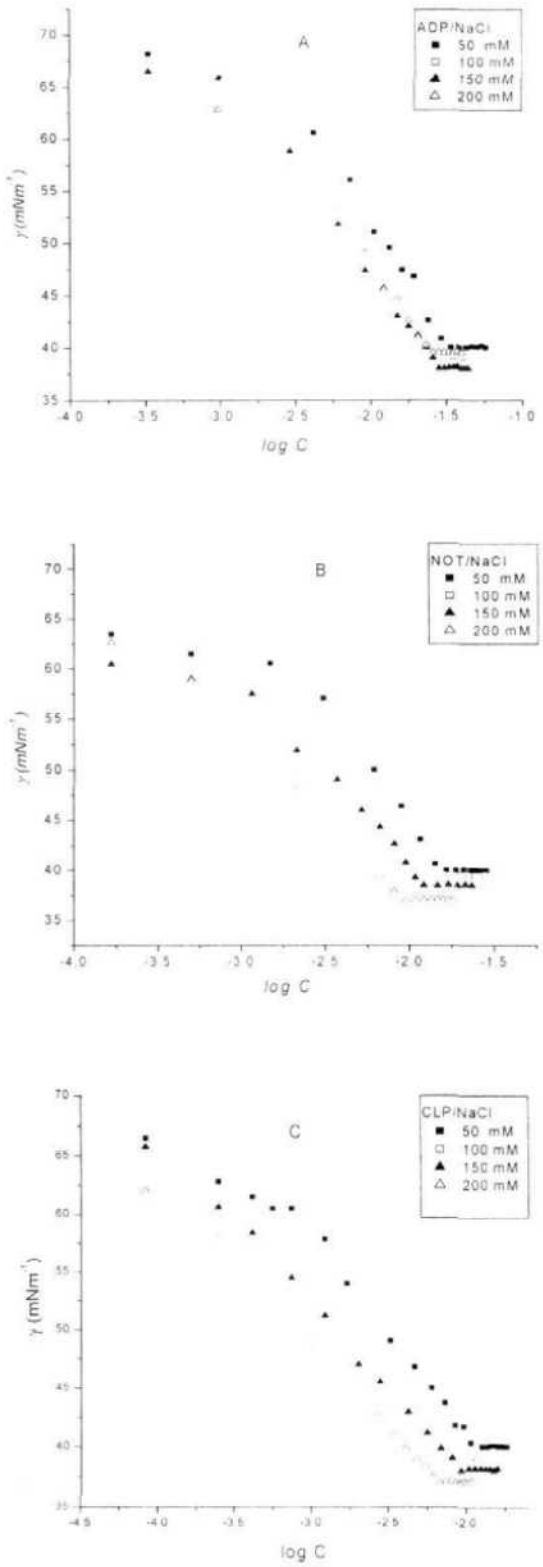


Fig. 3.29: *Plots of surface tension (γ) vs. log C of drugs in presence of different concentrations of NaCl.*

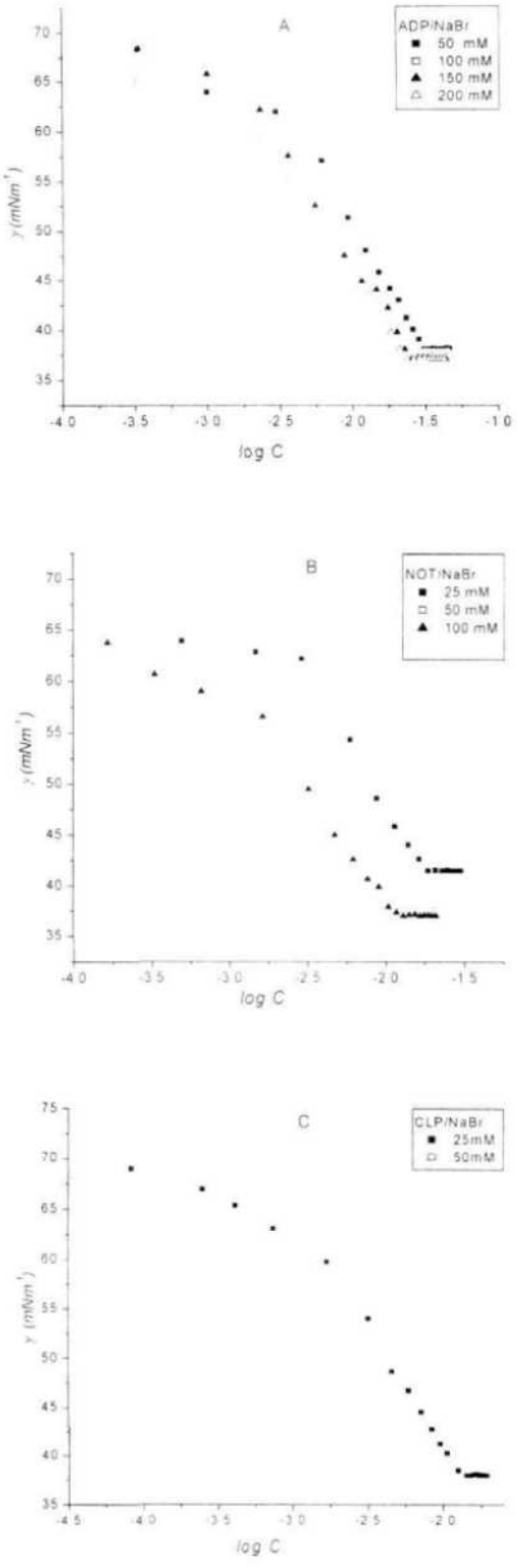


Fig. 3.30: *Plots of surface tension (γ) vs. log C of drugs in presence of different concentrations of NaBr.*

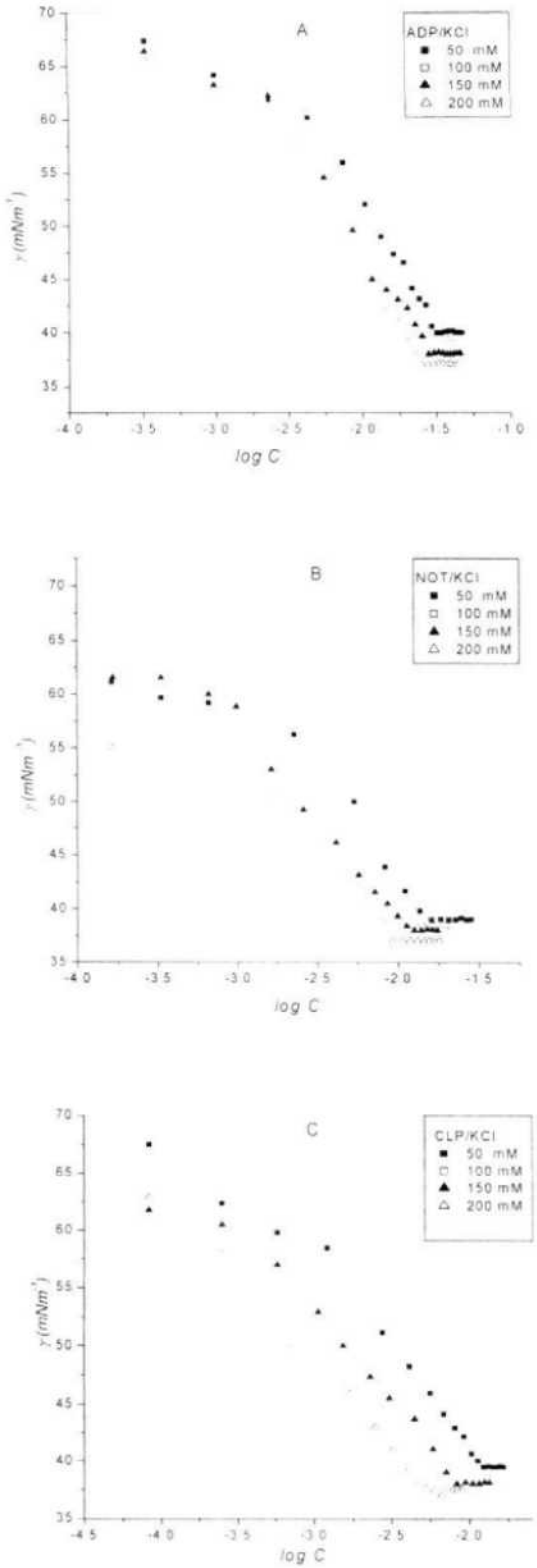


Fig. 3.31: *Plots of surface tension (γ) vs. log C of drugs in presence of different concentrations of KCl.*

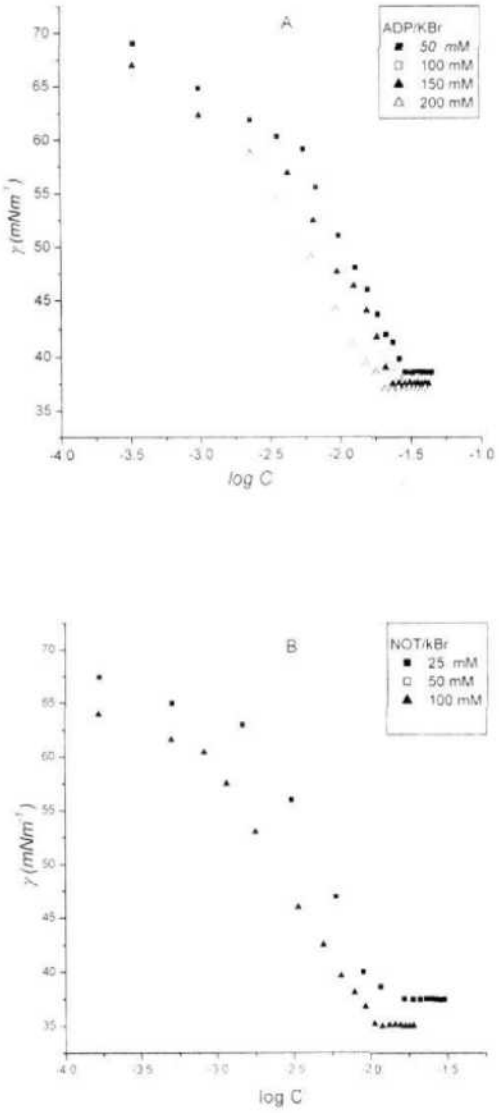


Fig. 3.32: *Plots of surface tension (γ) vs. log C of drugs in presence of different concentrations of KBr.*

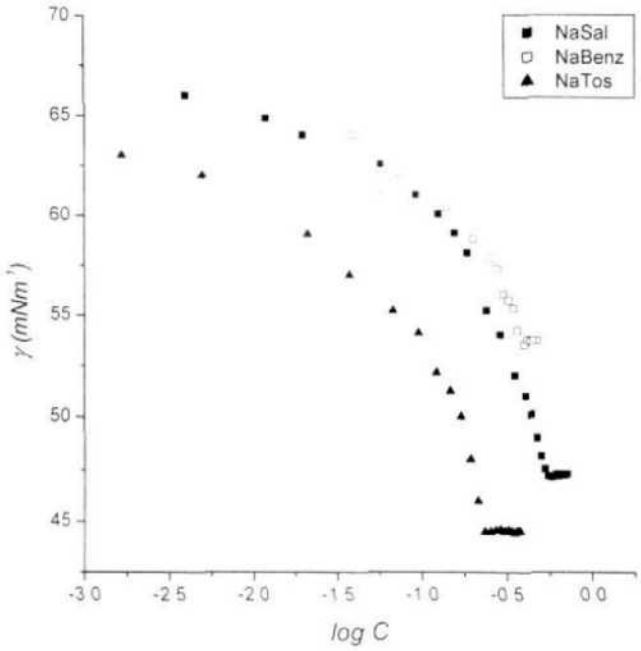


Fig. 3.33: *Plots of surface tension (γ) vs log C of pure hydrotropes (■ NaSal, □ NaBenz, ▲ NaTos).*

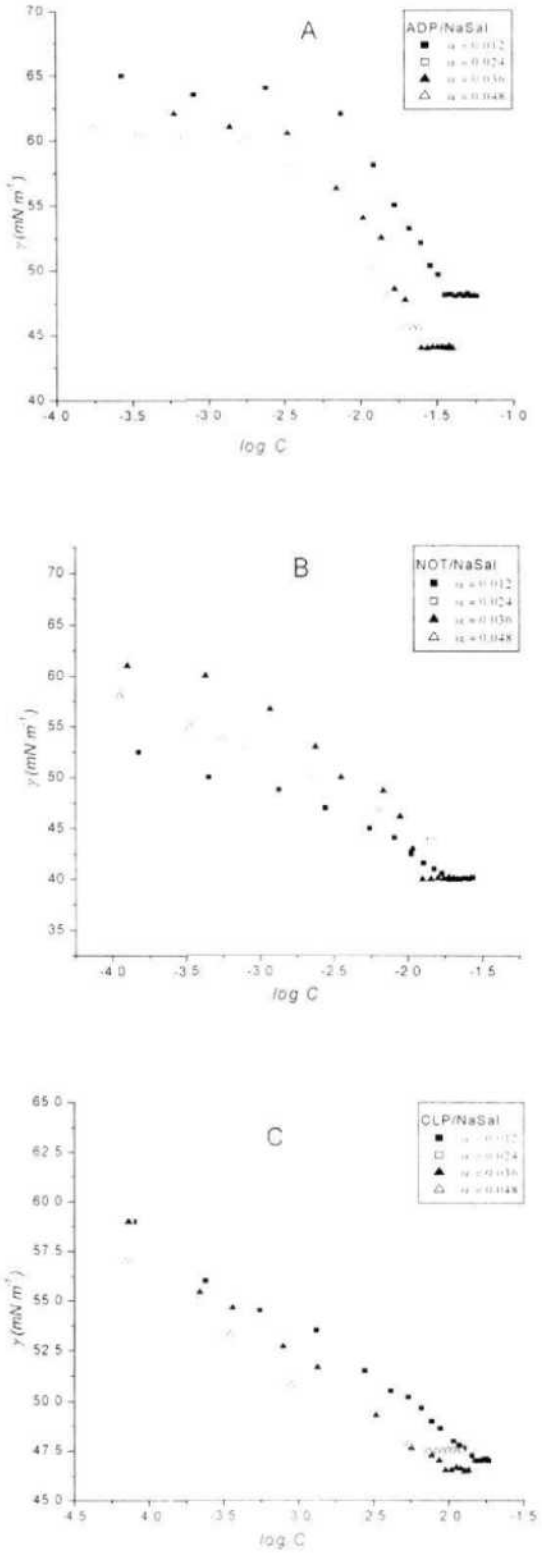


Fig. 3.34: *Plots of surface tension (γ) vs log C of NaSal with ADP (A), NOT (B) and CLP (C) at different mole fractions of NaSal (■ 0.012, □ 0.024, ▲ 0.036 and Δ 0.048).*

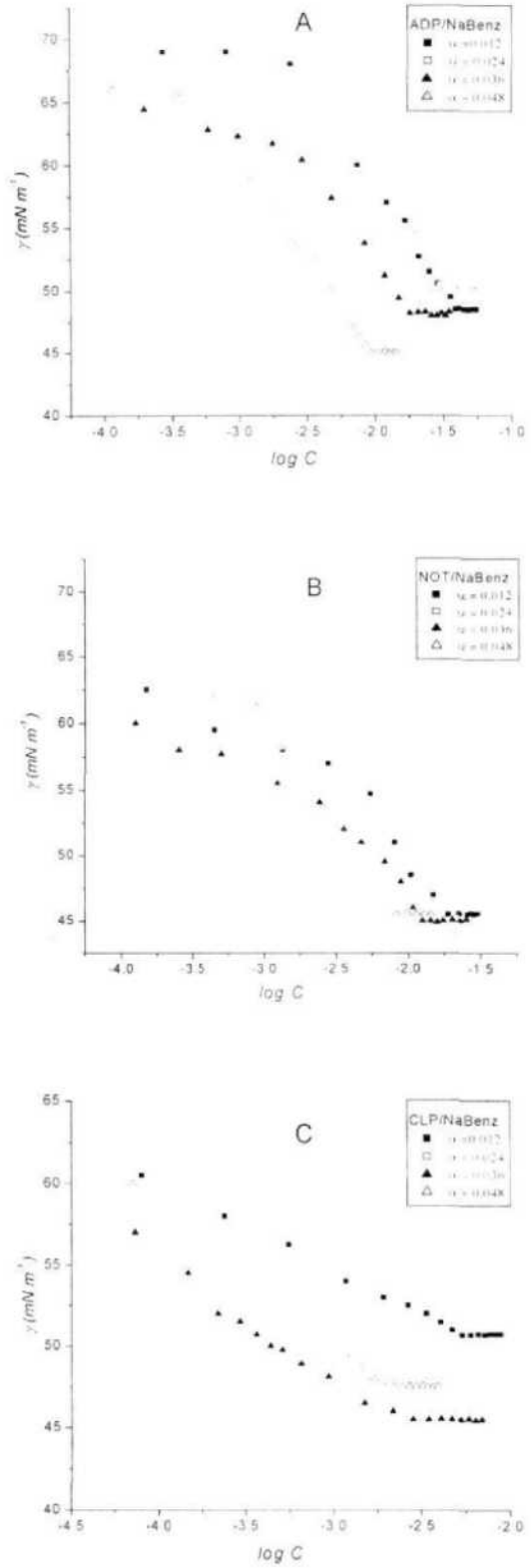


Fig. 3.35: *Plots of surface tension (γ) vs log C of NaBenz with ADP (A), NOT (B) and CLP (C) at different mole fractions of NaBenz (■ 0.012, □ 0.024, ▲ 0.036 and Δ 0.048).*

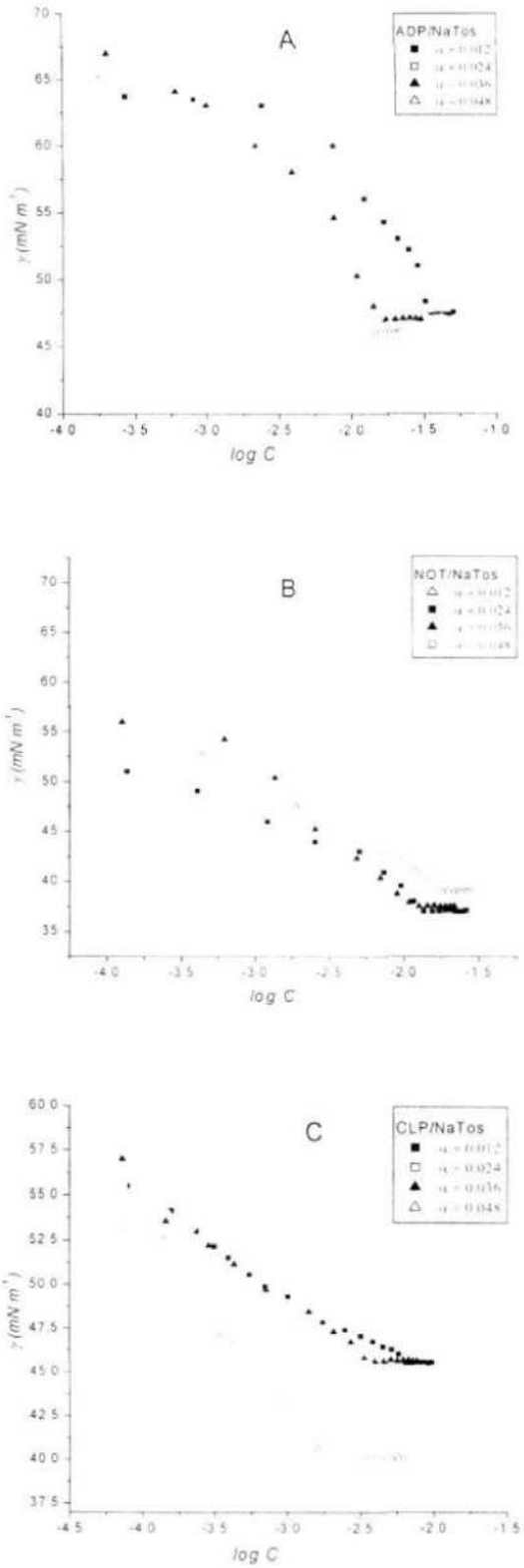


Fig. 3.36: *Plots of surface tension (γ) vs log C of NaTos with ADP (A), NOT (B) and CLP (C) at different mole fractions of NaTos (■ 0.012, □ 0.024, ▲ 0.036 and Δ 0.048).*

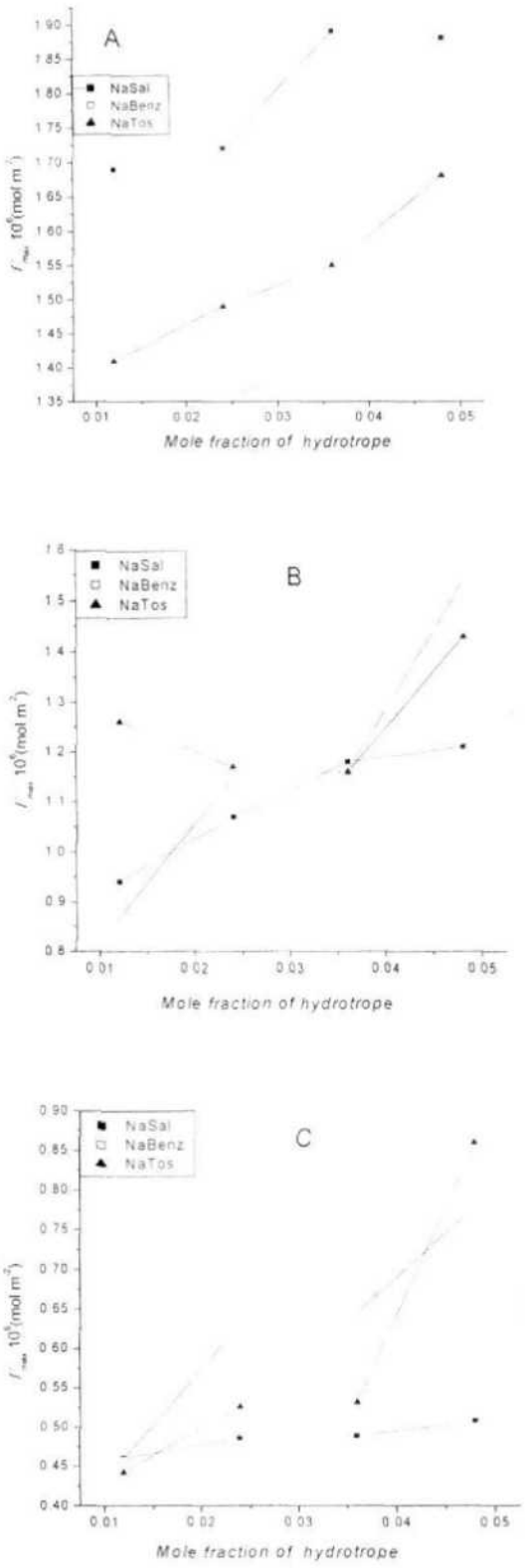


Fig. 3.37: *Variation of Γ_{max} with mole fraction of hydrotropes for ADP (A), NOT (B) and CLP (C)* (■ *NaSal*, □ *NaBenz* and ▲ *NaTos*).

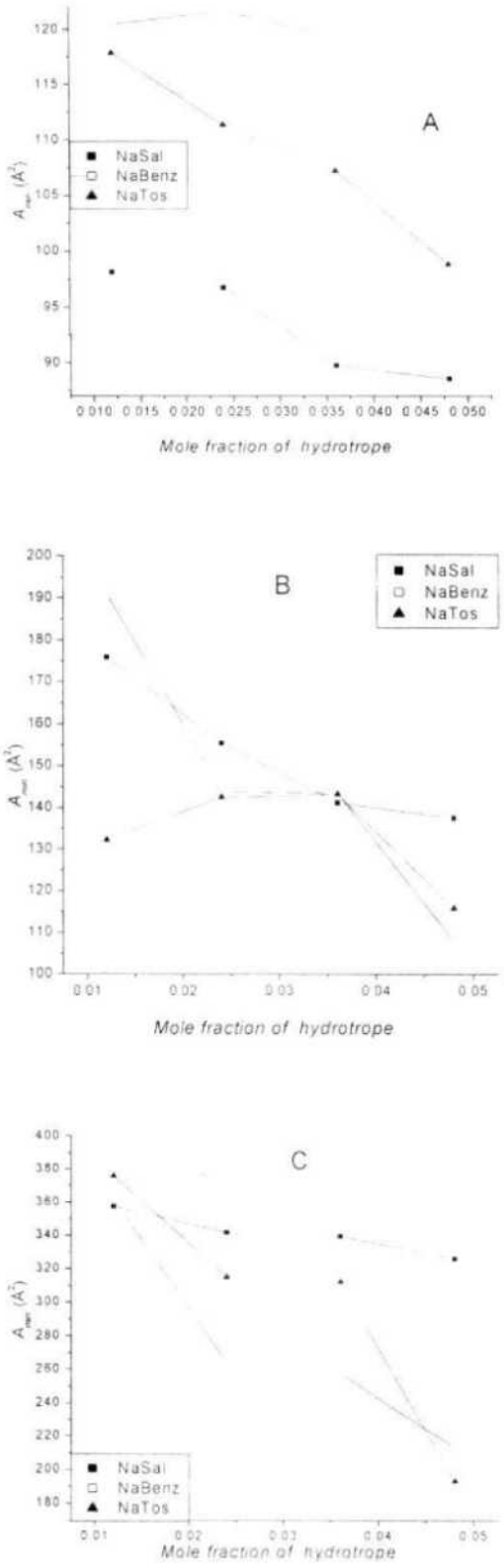


Fig. 3.38: *Variation of A_{min} with mole fraction of hydrotropes for ADP (A), NOT (B) and CLP (C) (■ NaSal, □ NaBenz and ▲ NaTos).*

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Chapter-IV

Solubilization of Phenytoin (PHT) by Cationic Gemini Surfactants (16-s-16 and 14-s-14, s = 4,5,6) and their Binary Mixtures with Nonionic Surfactants

Low aqueous solubility is usually a major hurdle in development of new pharmaceutical compounds as many problems like chemical solution preparation and designing of liquid drug formulation depend on drug's aqueous solubility. A large number of drugs fail to proceed beyond the initial stages because of their low aqueous solubility. Different methods used to modify drug solubility include use of cosolvents [1], selection of salt form [2], change of crystal form [3], preparation of solid dispersion [4], particle size reduction [5], complex formation [6,7] and use of prodrugs [8,9]. Micellar solubilization is another method for enhancing the drugs' solubility [10]. Micelles protect drugs from destructive factors upon parenteral administration, modify their biodistribution [11,12], and their (micelle) sizes permit them to accumulate in areas with leaky vasculature, at the same time avoiding uptake by reticulendothelial system [13]. Micellar formulation has less tendency of precipitation on dilution. They physically entrap sparingly soluble pharmaceuticals and deliver them to the desired site of action at concentration that can exceed their intrinsic aqueous solubility and thus can increase bioavailability. The undesirable side effects are lessened, as contact of the drug with inactivating species such as enzymes present in biological fluids are minimized, in comparison with free drug [14].

Common surfactants used in micellar formulation are either amphoteric, nonionic, copolymer or ionic. Micellar properties of nonionic surfactants depend mainly on the ability of hydrocarbon core of the micelles to dissolve a nonpolar solute. Thus, the solubilization capacity of the solute is controlled mainly by the

core volume. However, materials with some polarity such as benzoic acid, are absorbed at the interface between the core and the hydrophilic layer of the micelle [1]. Hence, the solubilization capacity is less controlled by the core and more dependent on the polar head group of the surfactants.

Saket [15] studied the micellar solubilization of mecolazine hydrochloride which is slightly water-soluble. The drug was solubilized in a series of different nonionic surfactant solutions, including Tweens and Brijs. The results showed that the longer the hydrocarbon chains in homologous series, the more efficient in the solubilizing power. Tween 80 is more efficient as solubilizer than Tween 20, and Brij 58 is more efficient than Brij 35, indicating that the drug is incorporated in the core more than the capsular region of the micelles.

Polymeric micelles are safer for parenteral administration than solubilizing agents currently in use like polyethoxylated castor oil (Cremophor EL) or polysorbate 80 (Tween 80) [16-19]. Polymeric micelles are kinetically stable so they dissociate slowly, even at concentrations below the *cmc*, extending circulation times in blood [19]. In addition, they have larger cores than surfactant micelles, leading to higher solubilization capacity than the regular micelles [19].

Gemini surfactants are better solubilizers [20-22] as they have better surface active properties than the corresponding conventional surfactants of equal chain length. Differently from conventional surfactants, gemini surfactants consist of two hydrophobic groups, two hydrophilic groups and spacer linked at or near head groups [23,24]. As a result, gemini surfactants form larger micelles than the

conventional surfactants and thus should have a better solubilizing capacity. The benefit of these surfactants (Tweens, copolymers and geminis) over traditional surfactants is potential for much lower *cmc's*. Amphiphiles having high cmc may not be suitable drug-targeting devices since they are unstable in an aqueous environment and easily dissociate upon dilution.

Phenytoin (PHT) was introduced in 1938 as an antiepileptic drug. It has the advantage over barbiturates in that it does not produce the sedation seen with those agents. Since its introduction, PHT has become the drug of choice in the treatment of grand mal epilepsy. Although the drug is commonly used orally for the chronic control of seizures, it is administered parenterally in certain instances. The intravenous route is recommended for the treatment of status epilepticus and the intramuscular route is recommended for prophylaxis against seizures or in patients who cannot take the drug orally [25]. The prophylactic use of PHT may be necessary in epileptic patients prior to surgery, to prevent seizures during neurosurgery or in preventing seizures which may result from acute bacterial meningitis [26].

The poor solubility of PHT has led to problems in both the formulation of suitable dosage forms and in achieving a uniform and predictable bioavailability. Since the drug is a weak acid with pK_a of 8.3 [27], it is largely unionized in the physiological pH range. The solubility of the unionized acid has been reported to be between 14 to 20.5 μg/ml [27,28]. The poor solubility of PHT is a result of its high melting point, 297 °C, and its highly hydrophobic nature. The bioavailability

of PHT by the oral route of the administration has been the subject of numerous studies. The drug is most commonly administrated as the sodium salt to further increase its solubility.

RESULTS AND DISCUSSION

Surfactant-surfactant interactions

The *cmc* values of the studied single as well as mixed surfactant systems are presented in Table 4.1, which were obtained from the plots shown in Figs. 4.1 and 4.2. The values for pure surfactants are in good agreement with the literature values. The ideal *cmc* values, *cmc** for mixed surfactant systems calculated using the Clint equation (3.1), are also included in Table 4.1 (Figs. 4.3 and 4.4). All the observed *cmc* values were found to be lower than ideal *cmc* values, indicating negative deviation from ideal behavior for the mixed micelle formation. The estimate of negative deviation of experimental *cmc* values from *cmc** and, hence, nonideality of mixed binary surfactant systems can be made in light of Rubingh's equation (3.3). The interaction parameter, β^m, accounts for deviation from ideality and is an indicator of the degree of interaction between two surfactants in mixed micelles. The values of β^m along with the micellar mole fraction, X_i^m, and activity coefficient, f_i^m, of the *i*th surfactant within mixed micelles calculated using Rubingh's treatment are presented in Table 4.1 for the selected equimolar binary surfactant systems. The negative values of β^m indicate synergistic interactions. It is well-known [30, 31] that for ionic-nonionic mixed surfactant systems significant

electrostatic self-repulsion of ionics and weak steric self-repulsion (depending on the head group size) of nonionics before mixing are weakened by dilution effects after mixing and that the electrostatic self-repulsion of the ionic surfactant is replaced by the ion-dipole interactions between the hydrophilic head groups of ionic and nonionic surfactants. Synergism in surfactant mixtures depends not only on the strength of interactions but also on the relevant properties of surfactants. Least synergism is observed with geminis-F108 and highest with geminis-Tween 40. F108, with polyoxyethylene (POE) groups, has a large number of oxygen atoms with lone pair of electrons. Thus, it should have a tendency to react coulombically with the cationic gemini surfactant; but the presence of long polyoxyethylene head group imposes some steric constraint due to thermal vibrations, restricting the effective head group interactions, hence showing lesser value of interaction parameter. The values of β^m were used to find activity coefficients of the components in micelles (f_1^m, f_2^m) (equations (3.5) and (3.6). The values of activity coefficients are less than unity in all systems indicating non-ideality in mixed micelles.

The liquid/air interface of a surfactant solution is well populated by the adsorbed molecules. The surfactant concentration is always more at the interface due to adsorption as compared to the concentration of the surfactant in the bulk. The maximum surface excess concentration at the air/water interface, Γ_{max}, was evaluated by the Gibbs adsorption equation (3.13) and eqoation (3.14) was used to

calculate the A_{min}. The values of Γ_{max} (and also of A_{min}) are given in Table 4.1. For mixtures of geminis-nonionic surfactants the value of n was 4 whereas for pure nonionic and gemini surfactant n was 1 and 3, respectively. The values of Γ_{max} in all systems were lower than that of nonionic surfactants, except in F108. The geminis have chain lengths of 14 and 16 carbons while Tween 40 and Tween 80 have 16 and 18 carbons in their tails. The dissimilarity in tail length with Tween 80 (with 18 carbons) is more than with Tween 40 (with 16 carbons). However, in Tween 80, presence of double bond slightly decreases the effect of chain length. On other hand the dissimilarity of the hydrophobic part of F108 poly (propyleneoxide) with geminis is more than the Tweens . When the chain lengths are dissimilar, the molecules above the height of adjacent molecules (of second component) will exhibit thermal motion. This thermal motion disturbs the surface causing loose packing (i.e., small Γ_{max}) and large area per head group. The A_{min} values for mixtures are greater than pure components. As the mixtures contain a gemini and nonionic surfactant, the Γ_{max} (or A_{min}) are expected to increase (or decrease). Adsorption of nonionic surfactant molecules between the positively charged molecules of gemini surfactants should decrease the repulsion among them and the inter head group distance should decrease. However, what we observed experimentally is an increase in A_{min}. The large hydrophilic group of Tweens and F108 as well as head-spacer-head configuration of geminis causes steric hindrance and the two molecules would be far apart from each other.

Although the intercalation of nonionic component between the two ionic surfactant molecules decreases the repulsion among them, the large hydrophilic group of nonionic component increases the overall area per head group.

The X_1^σ values (Table 4.2) are greater than α_1 and are smaller than X_1^m values. This means that the mixed micelles have greater contribution of nonionic surfactants than mixed monolayers. In other words, mixed monolayers contain more gemini as compared to mixed micelles. Rigid head group structure of geminis make it easier for them to accommodate at the planar air/water interface rather than to adjust in a curved micellar surface. Also, Tweens and F108 have long hydrophobic tails and adsorption of these surfactants on the interface with these long tails above the interface would make the surface unstable and hence these surfactants would prefer micelle formation.

The β^σ values are negative at all studied systems (Table 4.2), indicating attractive interactions among the components in the mixed monolayers.

Activity coefficients of the two components (f_1^σ, f_2^σ) are obtained by equations (3.11) and (3.12) and are listed in Table 4.2. These values are always less than unity suggesting nonideal mixing behavior. The f_1^σ values are greater than f_2^σ values indicating nonideality in the mixed monolayer

The values of excess Gibbs energy of micellization, ΔG_{ex}°, calculated by equation (3.7), are listed in Table 4.3. These values come out to be negative because stable mixed micelles are formed spontaneously.

The ΔG_m^o are negative indicating that the process of micelle formation is spontaneous. This is understandable as presence of nonionic surfactants in between the head groups of geminis reduces the electrostatic repulsion and makes the process more spontaneous. The ΔG_m^o values were further used to calculate ΔG_{ads}^o, the standard free energy of adsorption (using equation (3.16)), which are also negative and are larger in magnitude than ΔG_m^o. This suggests that molecules prefer to adsorb at the interface due to their hydrophobicity and after the saturation of interface these molecules aggregate to form micelles.

The G_{min} values, calculated by equation (3.15) (Table 4.3), come out to be positive. The lower the value, the more stable is the surface formed. Among pure components, Tween 40 forms most stable surface. Tween 40 has smallest chain which, although decreases the hydrophobicity of the molecule, makes its surface adsorption easier. Too long chain makes it difficult for the molecule to remain above water with the chain towards air.

Molar Solubilization Ratio (MSR) and Micelle Phase/Aqueous Phase Partitioning of PHT

A measure of the effectiveness of a surfactant in solubilizing a given solubilizate is the molar solubilization ratio (*MSR*) equivalent to increase in solubilizate concentration per unit increase in micellar surfactant concentration. In presence of excess of hydrophobic organic compound, *MSR*, given by the equation (4.1) [31-33]

$$MSR = ([S_t] - [S_{cmc}]) / (C_t - C_{cmc}) \quad (4.1)$$

is obtained from the slope of the curve that results when solubilizate concentration is plotted against surfactant concentration. $[S_t]$ is the total apparent solubility of PHT in single/mixed surfactant solutions at a particular total surfactant concentration, C_t, above *cmc* and $[S_{cmc}]$ is the apparent solubility of PHT at *cmc* which is taken as its water solubility, $[S_w]$, since it changes only very slightly up to the *cmc* of surfactant.

An alternative approach used to quantify the surfactant solubilization is based on the micelle-water partition coefficient (K_m), which represents the distribution of the organic compounds between surfactant micelles and the aqueous phase and may be expressed as follows [34]

$$K_m = X_m / X_a \quad (4.2)$$

where X_m and X_a are the mole fraction of solute in the micelle and aqueous phases, respectively. The value of X_m can be calculated using *MSR* by the equation (4.3)

$$X_m = MSR/(1+MSR) \quad (4.3)$$

The mole fraction of organic compound in the aqueous phase (X_a) was estimated as

$$X_a = [S_{cmc}].V_m \quad (4.4)$$

where V_m is the molar volume of water (0.01807 d m^3/mol) at 30 °C. With these expressions, K_m becomes

$$K_m = MSR/\{[S_{cmc}]V_m(1+MSR)\} \quad (4.5)$$

The aqueous solubility of PHT increases linearly over the range of single or mixed surfactant concentrations above *cmc* indicating its solubility enhancement in water. The *MSR* calculated from equation (4.1) and K_m of PHT in gemini-nonionic surfactants with equimolar mixtures are listed in Table 4.4. Among the single surfactant systems, *MSR* is found to be in the order F108 > Tween 80 >Tween 40 >16-6-16 >16-5-16 >16-4-16 >14-6-14 >14-5-14 >14-4-14 and K_m also found to be in order F108 >Tween 80 >Tween 40, 16-6-16 >16-5-16 >16-4-16, 14-6-14 >14-5-14 >14-4-14. Higher solubilization power of F108 compared to Tween 80 and Tween 40 may be due to the greater number of oxyethylene (OE) units in it, which may facilitate solubilization of the drug due to hydrogen bonding between PHT and (OE) head groups at the interfacial region. On the other hand, the higher solubilization power of Tween 80 compared to Tween 40 may be referred to hydrocarbon chain length of hydrophobic part of surfactant [15]. Nonionic surfactants F108 and Tweens have higher *MSR* and K_m for PHT than the cationic surfactants (16-s-16 and 14-s-14).

Solubility of PHT in mixed 16-s-16/nonionic and 14-s-14/nonionic surfactants systems were determined and compared with those in the single surfactants systems. The plots of solubility of PHT against total surfactant concentrations in 16-s-16 / nonionic and 14-s-14 / nonionic surfactant systems are presented in Figs. 4.5 to 4.7. It observed that the *MSR* and K_m values (Table 4.4) of

PHT in mixed surfactant is higher than those in single surfactant solutions except F108 in some cases. This may be due the large effective solubilization area in the mixed micelles than that of single surfactant systems as a result of an increase in the radius of the mixed micelles including the electric dipole [35].

Treiner and coworkers [36-38] have suggested that the partition coefficient of natural organic solute between micelle and aqueous phase in mixed surfactants may be represented by the relationship

$$ln\, K_{m12} = X_1^m\, lnK_{m1} + (1-X_1^m) ln\, K_{m2} + BX_1^m\,(1-X_1^m) \qquad (4.6)$$

where K_{m12}, K_{m1} and K_{m2} are the micelle-water partition coefficients of the solute in mixed and single surfactant systems, respectively, and X_1^m (X_2^m) represents the micelle mole fraction of surfactant 1(2). As per Zhou and Zhu [39], B is an empirical parameter that incorporates both the surfactant-surfactant (as in β^m) and surfactant–solute interactions. When $B = 0$, mixing has no effect on the partitioning of solute, but $B > 0$ or $B < 0$ implies that K_m in the mixed surfactant system is larger than that predicted by ideal mixing rule.

Table 4.4 lists the values of B evaluated for the studied equimolar binary surfactant systems. The values of B are found to be positive for the all surfactant mixtures. Here, there is no distinct relationship between the values of B and β^m, because the value of B must depend both on surfactant-surfactant and surfactant-solute interactions in the mixed micelles. Further understanding of the mixing effect of the gemini-nonionic surfactants on solubilization of PHT is made on the

basis of the deviation ratio (R) between the experimental molar solubilization (MSR_{exp}) and the ideal value (MSR_{ideal}), evaluated by $R = MSR_{exp}/MSR_{ideal}$, where $MSR_{ideal} = \Sigma_i MSR_i \alpha_i$. ($MSR_i$ is the experimental MSR value of the solubilizate in the pure ith surfactant solution whose bulk mole fraction in the mixture is α_i). The $R >$ 1 values (Table 4.4) imply positive mixing effect of surfactants on solubilization. All binary systems have R values greater than unity. In case of cationic-nonionic surfactant systems, a slight positive charge developed on the mixed micellar surface facilitates micelle-water interface adsorption in addition to micellar core solubilization, resulting in the value of R greater than unity.

Since B and R values are direct outcome of the individual K_m and MSR values respectively, correlation between the former two parameters is expected which is evident from Table 4.4. In spite of the disagreement between the values of R and B, both indicate positive deviation from ideality and reveal that the synergistic surfactant mixing, as indicated by the negative β^m value (Table 4.1) enhanced the solubilization of PHT.

Thermodynamics of Solubilization

From the thermodynamic point of view, solubilization can be considered as normal partitioning of the PHT between two phases, micelle and aqueous, and the standard free energy of solubilization, ΔG_s^o, can be represented by the expression [40]

$$\Delta G_s^o = -RT \ln K_m \qquad (4.7)$$

Here R is the gas constant and T the absolute temperature. The ΔG_S^o values thus calculated are presented in Table 4.4. For all the systems, the ΔG_S^o values come out to be negative indicating spontaneous solubilization. Among the pure surfactants the absolute ΔG_S^o value is the highest for F108, whereas in mixed systems the ΔG_S^o values are found to be higher than the pure, suggesting more solubilization of PHT.

Table 4.1: *Critical micelle concentration (cmc), ideal cmc (cmc*), micellar composition (X_1^m), interaction parameter (β^m), activity coefficients (f_i^m), surface excess (Γ_{max}) and minimum area per head group (A_{min}) of equimolar binary surfactant mixtures of gemini +nonionic surfactants at 30 °C.*

Surfactant system	*cmc* (mM)	$\Gamma_{max}.10^6$ (mol m^{-2})	A_{min} (Å^2)	Mixed surfactant system	*cmc* (mM)	*cmc** (mM)	$\Gamma_{max}.10^6$ (mol m^{-2})	A_{min} (Å^2)	β^m	X_1^m/X_2^m	f_1^m/f_2^m
16-4-16	0.028	1.62	102.73	16-4-16/T40	0.013	0.028	0.55	299.56	-3.21	0.50/0.49	0.45/0.46
16-5-16	0.032	1.41	118.19	16-4-16/T80	0.011	0.018	0.65	257.10	-2.07	0.60/0.40	0.72/0.47
16-6-16	0.038	1.24	134.50	16-4-16/F108	0.021	0.031	0.52	316.49	-1.56	0.47/0.52	0.65/0.70
14-4-14	0.141	1.52	108.93	16-5-16/T40	0.015	0.030	0.59	278.49	-2.88	0.52/0.48	0.52/0.46
14-5-14	0.161	1.48	112.15	16-5-16/T80	0.019	0.019	0.58	284.75	-1.59	0.62/0.37	0.80/0.54
14-6-14	0.192	1.44	115.31	16-5-16/F108	0.032	0.021	0.52	317.79	-1.77	0.49/0.50	0.63/0.65
F108	0.034	0.75	220.58	16-6-16/T40	0.014	0.032	0.61	271.09	-2.65	0.54/0.46	0.57/0.46
T80	0.028	3.18	55.26	16-6-16/T80	0.011	0.019	0.58	282.74	-2.65	0.62/0.38	0.68/0.36
T40	0.013	2.51	66.32	16-6-16/F108	0.017	0.036	0.52	316.85	-3.78	0.51/0.49	0.40/0.37
				14-4-14/T40	0.034	0.047	0.67	248.19	-1.84	0.71/0.28	0.86/0.39
				14-4-14/T80	0.020	0.024	0.71	234.74	-1.58	0.81/0.18	0.95/0.35
				14-4-14/F810	0.051	0.051	0.58	286.57	-0.53	0.76/0.23	0.97/0.73
				14-5-14/T40	0.035	0.048	0.68	242.29	-1.93	0.73/0.26	0.86/0.36

14-5-14/T80	0.022	0.024	0.67	246.31	-0.97	0.86/0.14	0.98/0.48
14-5-14/F108	0.051	0.056	0.58	283.76	-0.65	0.75/0.24	0.97/0.67
14-6-14/T40	0.037	0.049	0.67	247.19	-1.85	0.79/0.21	0.88/0.36
14-6-14/T80	0.021	0.024	0.62	266.31	-1.53	0.84/0.16	0.96/0.34
14-6-14/F108	0.052	0.059	0.52	283.76	-0.73	0.79/0.21	0.97/0.63

Table 4.2: *The surface composition (X_1^σ), interaction parameter (β^σ) and activity coefficients (f_1^σ) of binary surfactant mixtures of gemini + nonionic surfactants at 30 °C.*

System	X_1^σ	β^σ	f_1^σ	f_2^σ
16-4-16/T 40	0.56	-3.29	0.53	0.35
16-4-16/T80	0.60	-3.81	0.55	0.25
16-4-16/F108	0.59	-1.57	0.77	0.58
16-5-16/T40	0.58	-4.31	0.47	0.23
16-5-16/T80	0.65	-3.20	0.67	0.26
16-5-16/F108	0.66	-1.04	0.88	0.64
16-6-16/T40	0.58	-4.61	0.44	0.21
16-616/T80	0.64	-3.76	0.61	0.21
16-6-16/F108	0.59	-3.59	0.55	0.29
14-4-14/T40	0.68	-4.66	0.62	0.12
14-4-14/T80	0.74	-4.12	0.76	0.10
14-4-14/F108	0.76	-2.34	0.87	0.26
14-5-14/T40	0.70	-3.46	0.73	0.18
14-5-14/T80	0.70	-5.30	0.61	0.08
14-5-14/F108	0.69	-3.80	0.69	0.17
14-6-14/T40	0.66	-4.54	0.59	0.14
14-6-14/T80	0.69	-5.26	0.60	0.08
14-6-14/F108	0.74	-2.16	0.86	0.31

Table 4.3: *Various thermodynamic parameters (ΔG°_{ex}, ΔG°_{m}, G_{min} and ΔG°_{ads}) for 16-s-16 /14-s-14 + nonionic mixed surfactant systems at 30 °C.*

Mole fraction	ΔG°_{ex} (kJ mol^{-1})	ΔG°_{m} (kJ mol^{-1})	G_{min} (kJ mol^{-1})	ΔG°_{ads} (kJ mol^{-1})
16-4-16/T40				
0		-36.5	25.9	-54.0
0.5	-2.0	-38.5	55.3	-88.7
1		-36.6	15.2	-50.3
16-4-16/T80				
0.5	-1.2	-38.8	61.2	-92.1
1		-38.4	12.3	-48.2
16-4-16/F108				
0.5	-1.0	-37.2	74.2	-96.9
1		-36.0	51.1	-79.0
16-5-16/T40				
0		-36.2	29.7	-56.1
0.5	-1.8	-38.1	55.3	-88.7
1		-36.6	15.2	-50.3
16-5-16/T80				
0.5	-0.9	-38.5	55.3	-82.3
1		-38.4	12.3	-48.2
16-5-16/F108				
0.5	-1.1	-37.2	69.1	-88.7
1		-36.0	51.1	-79.0
16-6-16/T40				
0		-37.6	33.5	-51.3
0.5	-1.7	-38.3	57.4	-85.9
1		-36.6	15.2	-50.3
16-6-16/T80				
0.5	-1.6	-38.9	57.7	-89.5
1		-38.4	12.3	-48.2
16-6-16/F108				
0.5	-2.6	-37.8	64.8	-96.1
1		-36.0	51.1	-79.0

Contd...

14-4-14/T40				
0		-32.4	27.2	-51.1
0.5	-3.0	-35.0	53.7	-98.0
1		-36.6	15.2	-50.3
14-4-14/T80				
0.5	-2.3	-37.4	57.1	-102.8
1		-38.4	12.3	-48.2
14-4-14/F108				
0.5	-2.7	-35.0	68.9	-99.7
1		-36.0	51.1	-79.0
14-5-14/T40				
0		-32.1	25.8	-55.6
0.5	-2.9	-35.9	60.5	-96.4
1		-36.6	15.2	-50.3
14-5-14/T80				
0.5	-3.5	-37.1	59.2	-101.4
1		-38.4	12.3	-48.2
14-5-14/F108				
0.5	-2.6	-35.0	70.9	-101.9
1		-36.0	51.1	-79.0
14-6-14/T40				
0		-31.7	25.9	-56.2
0.5	-2.8	-35.8	64.9	-100.8
1		-36.6	15.2	- 50.3
14-6-14/T80				
0.5	-3.3	-37.2	51.3	-94.3
1		-38.4	12.3	-48.2
14-6-14/F108				
0.5	-2.5	-34.9	66.7	-107.4
1		-36.0	51.1	-79.0

Table 4.4: *Molar solubilization ratio (MSR), ln K_m, free energy of solubilization (ΔG_S°), deviation ratio (R), and experimental interaction parameter (B) for single and binary surfactant systems at 30 °C.*

System	MSR_{exp}/MSR_{ideal}	$ln\ K_m$	R	B	ΔG_S° (kJ mol^{-1})
T40	0.0786	11.35			-28.5
T80	0.0821	11.39			-28.6
F108	0.1095	11.65			-29.3
16-4-16	0.0754	11.31			-28.4
16-5-16	0.0756	11.46			-28.8
16-6-16	0.0761	11.47			-28.8
14-4-14	0.0625	11.26			-28.3
14-5-14	0.074	11.44			-28.7
14-6-14	0.0748	11.45			-28.7
16-4-16/T40	0.1014/0.077	11.58	1.32	1.02	-29.1
16-4-16/T80	0.1066/0.079	11.63	1.36	1.20	-29.2
16-4-16/F108	0.1199/0.092	11.73	1.29	0.96	-29.4
16-5-16/T40	0.0851/0.077	11.59	1.10	0.43	-29.1
16-5-16/T80	0.0974/0.079	11.73	1.24	1.03	-29.5
16-5-16/F108	0.1484/0.093	12.20	1.60	2.14	-30.6
16-6-16/T40	0.1510/0.077	12.22	1.95	2.97	-30.7
16-6-16/T80	0.1301/0.072	12.05	1.64	2.35	-30.3
16-6-16/F108	0.1491/0.093	12.21	1.61	2.18	-30.6
14-4-14/T40	0.0928/0.071	11.68	1.32	1.74	-29.3
14-4-14/T80	0.0933/0.072	11.69	1.29	2.47	-29.3
14-4-14/F108	0.1139/0.086	11.91	1.32	2.82	-29.9
14-5-14/T40	0.1008/0.076	11.77	1.32	1.58	-29.6
14-5-14/T80	0.1150/0.078	11.92	1.47	3.89	-29.9
14-5-14/F108	0.1368/0.092	12.11	1.49	3.30	-30.4
14-6-14/T40	0.1013/0.077	11.78	1.32	1.65	-29.6
14-6-14/T80	0.1192/0.078	11.96	1.52	3.65	-30.0
14-6-14/F108	0.1462/0.092	12.18	1.59	3.92	-30.6

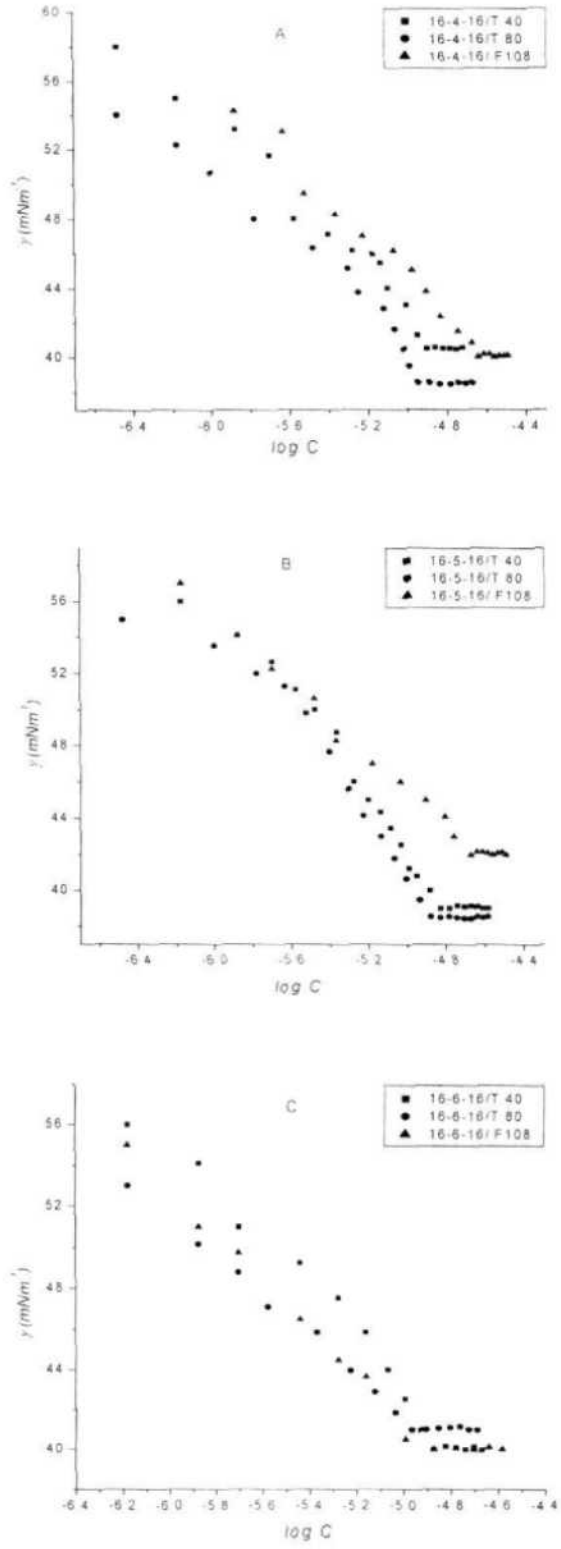

Fig. 4.1: *Plots of surface tension (γ) vs. log C of nonionic surfactants with 16-4-16 (A), 16-5-16 (B) and 16-6-16 (C) (■ T 40, • T 80 and ▲ F108).*

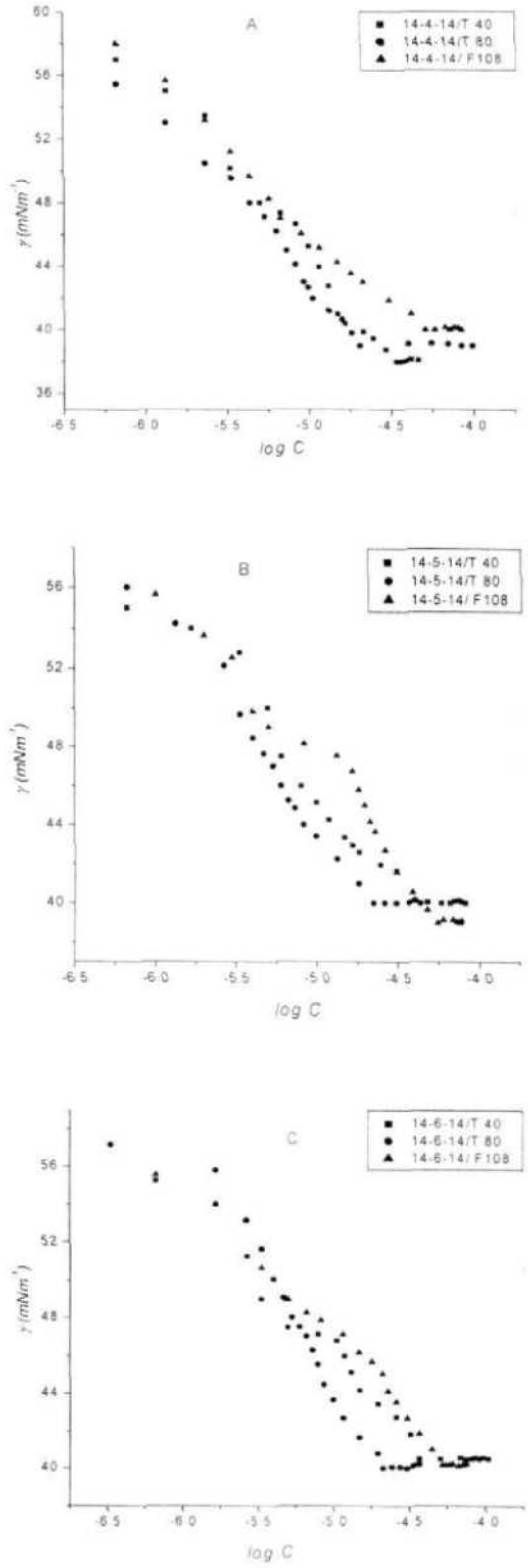

Fig. 4.2: *Plots of surface tension (γ) vs. log C of nonionic surfactants with 14-4-14 (A), 14-5-14 (B) and 14-6-14 (C) (■ T 40, • T 80 and ▲ F108).*

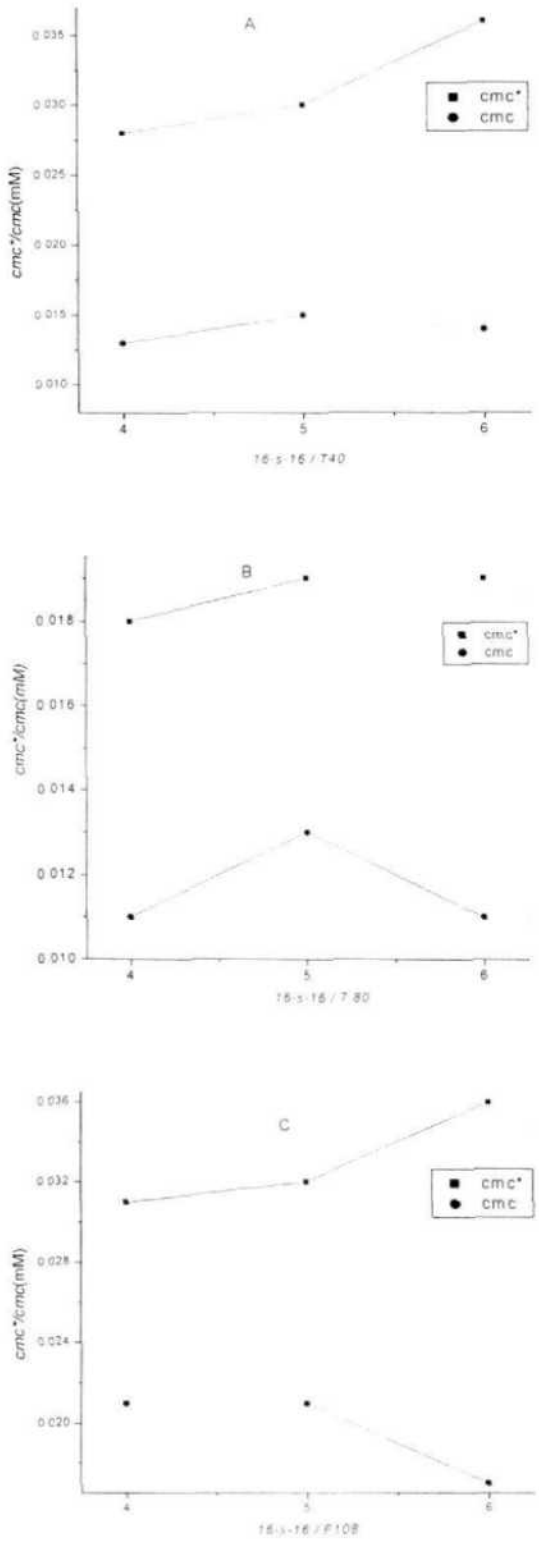

Fig. 4.3: *Plots of (■ cmc * and • cmc) vs. spacer of geminis 16-s-16 with T 40 (A), T 80 (B) and F108 (C).*

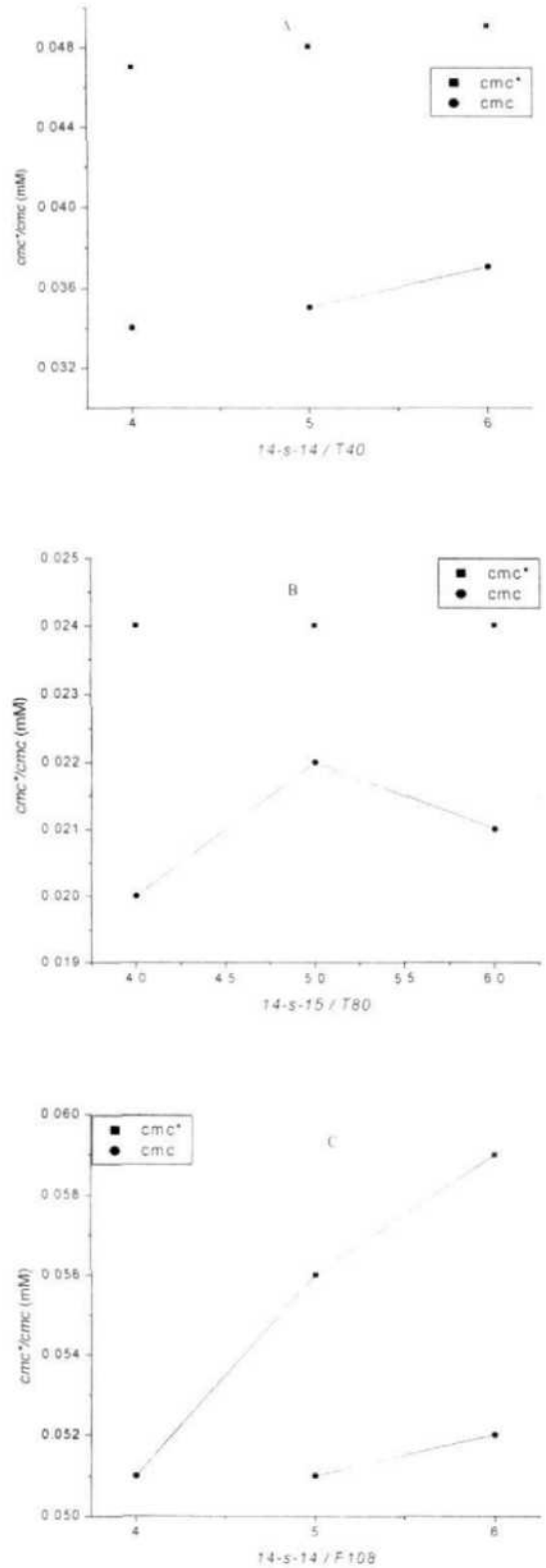

Fig. 4.4: *Plots of (■ cmc* and • cmc) vs. spacer of geminis 14-s-14 with T 40 (A), T 80 (B) and F108 (C).*

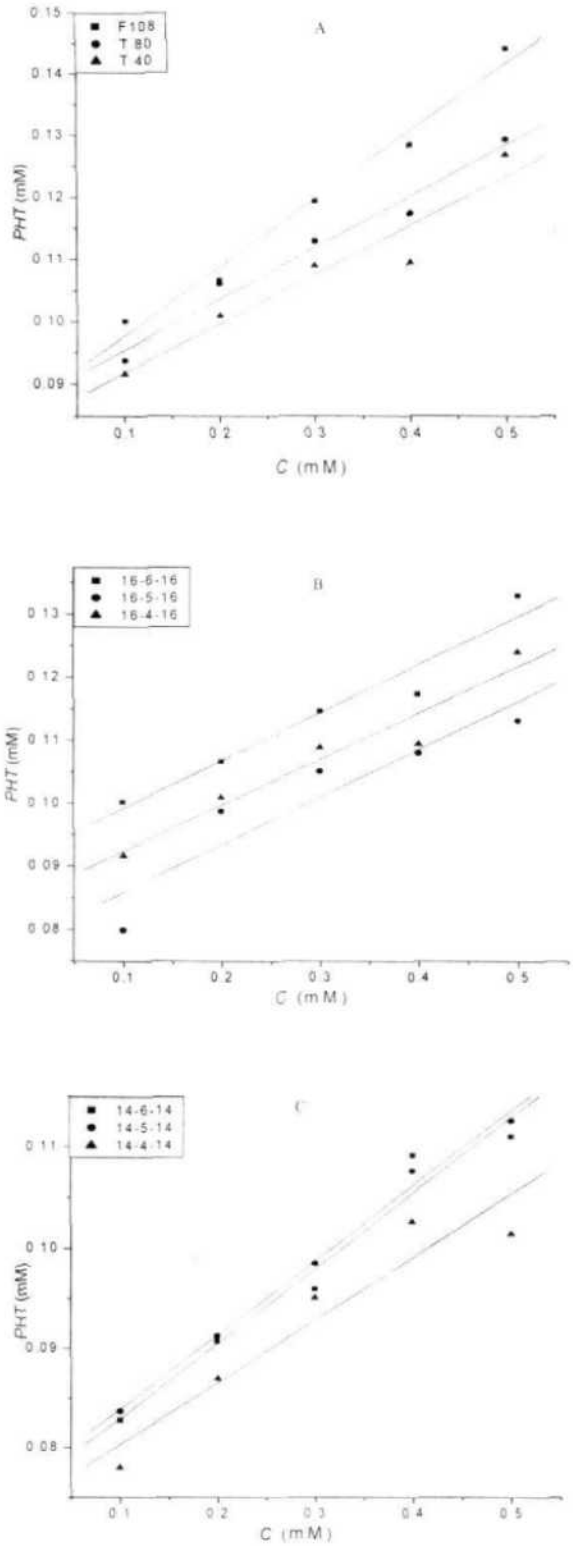

Fig. 4.5: *Variation of solubility of PHT in: A) ■ F108, • T 80 and ▲T 40, (B) ■ 16-6-16, • 16-5-16 and ▲16-4-16 (C) ■ 14-6-14, • 14-5-14 and ▲14-4-14.*

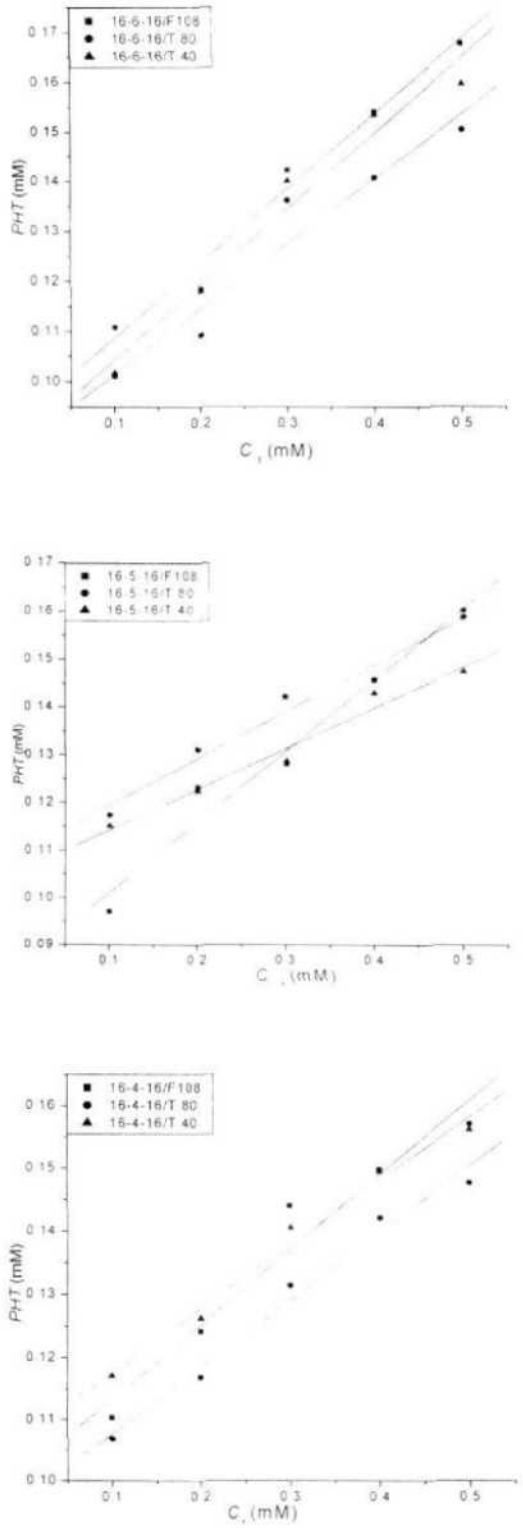

Fig. 4.6: *Variation of solubility of PHT with total surfactant concentration (C_t) of binary 16-s-16 /nonionic surfactant combinations.*

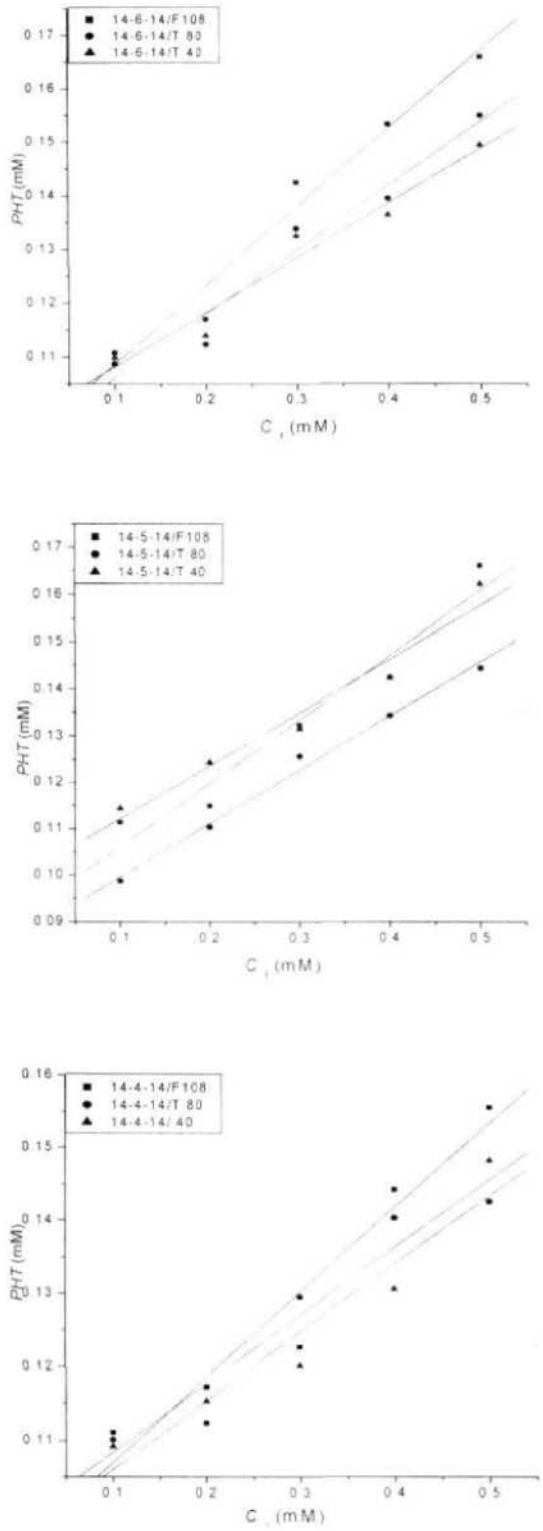

Fig. 4.7: *Variation of solubility of PHT with total surfactant concentration (C_t) of binary 14-s-14/nonionic surfactant combinations.*

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